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Cleveland Clinic Quarterly

A Bulletin Published by

The Staff of the Cleveland Clinic

CLEVELAND, OHIO

Vol. 10 JULY, 1943 No. 3

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CLEVELAND CLINIC QUARTERLY

Issued in four numbers during the year; one in January, one in April, one in July and one in October, by Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland, Ohio.

Entered as second-class matter March 4, 1935, at the Post Office at Cleveland, Ohio, under the Act of August 24, 1912.

CLINICAL AND PATHOLOGIC CRITERIA AS A BASIS FOR CLASSIFYING CASES OF PRIMARY CANCER OF THE BREAST

U. V. PORTMANN, M.D.

It is only by classifying cases of cancer that comparisons of the results of different therapeutic procedures can be analyzed equitably. There are many reports in the medical literature about the results of treatment of cancer of the breast in which cases are not classified, and therefore unjustifiable conclusions are drawn. Also, in some reports either clinical or pathologic criteria are the basis for statistical analyses. None of these classifications has been entirely satisfactory or generally accepted because of limited applicability.

Classification based solely on histologic criteria, such as one outlined by Ewing[1] or the "grading" plan of Broders,[2] is unsatisfactory because the histologic structure of most, if not all, of these neoplasms varies in many areas. The histologic name, or grade, given a tumor is subject to individual interpretation of microscopic sections examined but does not describe the whole tumor or the anatomic extent of involvement. Also, patients will survive with cancers considered to be highly malignant from the histology, whereas others will succumb from neoplasms of seemingly low degree of malignancy depending upon anatomic extent of involvement and whether or not the cancers can be eradicated.

Another classification has been based primarily upon pathologic evidence of the presence or absence of metastases in axillary lymph nodes. However, the degree of axillary involvement is most important. Also, there are other clinical and pathologic manifestations of prognostic significance.

Classifications of cases of cancers of the breast based only upon clinical criteria, such as those suggested by Steinthal,[3] Lee and Stubenbord,[4] and the American College of Surgeons,[5] have limited applicability. Physical signs alone may not indicate the extent of involvement. For example, the presence or absence of metastasis to axillary lymph nodes or elsewhere often cannot be settled clinically or even grossly at operation, yet is of considerable prognostic significance. The presence of metastases to axillary lymph nodes can be detected clinically in only about 50 per cent of cases proven to have metastases by microscopic examinations after radical mastectomies.

Another clinical classification of cases designates two groups as "operable" and "inoperable." This method, more than any other, has

been responsible for misunderstandings and controversies about the efficacy of different methods of treatment. These terms are ambiguous; surgeons cannot agree about their definitions because of different interpretations of the clinical signs, sometimes according to estimates of surgical skill. All cancers of the breast are technically "operable," and every Doctor of Medicine is legally qualified to operate. The terms "operable" and "inoperable" should be discarded, and "surgically curable" and "surgically incurable" substituted.

It must be conceded that the anatomic extent of involvement from cancer is the most important factor governing indications for and limitations of therapeutic procedures, curability or incurability, and therefore is the most logical basis for classifying cases. Anatomic extent of involvement can be ascertained best by taking into account all information available from both clinical and pathologic evidence.

When studying a series of cases of cancer of the breast 7 years ago for statistical analyses of the results and comparison of different methods of treatment, I used several of the methods of classification mentioned and found that none were suitable for the reasons indicated. After correlating the clinical findings with the pathologic evidences of extent of involvement, a new classification was developed with the cooperation of Dr. Allen Graham, Director of the Department of Surgical Pathology.

According to this plan cases were divided into three groups, or stages, on the basis of both clinical and pathologic criteria.[6, 7, 8] Subsequently, it was found advisable to subdivide the third group to make a fourth for cases having physical or roentgenologic signs of distant metastases when first examined.[9] The reason for this designation of a fourth group is that the results of operations alone cannot be compared with those of irradiation for patients with distant metastases because operations with the objective to cure are not performed but irradiation may be given for palliation.

In its present improved form the classification being proposed for primary cases of cancer of the breast is arranged as follows:

Group or Stage I

Skin—not involved.
Tumor—localized in breast and movable.
Metastases—none in axillary lymph nodes or elsewhere.

Group or Stage II

Skin—not involved.
Tumor—localized in breast and movable.
Metastases—few axillary lymph nodes involved, no other metastases.

Group or Stage III

Skin—edematous; brawny red induration and inflammation not obviously due to infection; extensive ulceration; multiple secondary nodules.

Tumor—diffusely infiltrating breast; fixation of tumor or breast to chest wall; edema of breast; secondary tumors.

Metastases—many axillary lymph nodes involved or fixed; no clinical or roentgenologic evidences of distant metastases.

Group or Stage IV

Skin—as in any other group or stage.

Tumor—as in any other group or stage.

Metastases—axillary and supraclavicular lymph nodes extensively involved, and clinical or roentgenologic evidences of more distant metastases.

When this classification was applied to a series of 1000 cases of cancer of the breast, the incidence of each group, or stage, and the 5 year survival rates were found to be approximately as follows:

Incidence	Survival Rates	
	Operations only	Operation and Irradiation
Group I —25%	90%	90%
Group II —25%	50%	65%
Group III—30%	5%	15%
Group IV—20%	5%	10%

This analysis not only proved the applicability and equitability of this classification for statistical comparisons, but also explained the indications for and limitations of different methods of treatment.

Group I—It seldom is possible to distinguish clinically between benign and malignant tumors of the breast that are small, localized, and movable if the skin is normal and no enlarged axillary nodes are palpable. Excision (not incision) and immediate microscopic examinations are indicated. Radical mastectomies may be indicated when tumors are found to be malignant to ascertain whether or not axillary lymph nodes are involved. Every node removed should be examined microscopically.

In 25 per cent of the cases having radical mastectomies, metastases to axillary nodes were not demonstrated. Of these approximately 90 per cent survived 5 years without clinical evidence of cancer whether or not irradiation was given. But about 10 per cent were not cured. Some of these had cancers that did not metastasize to axillary nodes but elsewhere, as may happen especially from inner quadrant tumors which may extend primarily to the parasternal nodes; in others neoplastic

cells may have passed through the axillary nodes to lodge in other regional groups; in a few axillary metastases may have escaped the careful scrutiny of the pathologist.

Since patients without axillary metastases (Group I) rarely develop local recurrences, and since there was no difference in the high percentage of survivals of those having operations alone and those having operation plus irradiation, it was concluded that immediate postoperative irradiation is unnecessary for patients in this category.

Group II—There is adequate statistical evidence that the prognosis is less favorable for patients with small, localized, movable cancers of the breast, without skin or muscle involvement and with metastases in only a few axillary lymph nodes, than for patients with similar tumors but with no axillary extension. In some with small cancers one or two quite large nodes may be palpable and no others involved, but in a majority with few nodes involved the condition cannot be detected clinically but only at operation or by microscopic examination.

These cases are on the borderline between curability and incurability. In our series 25 per cent of the patients having radical mastectomies alone had localized tumors, not involving skin or muscle but with metastases in only a few axillary lymph nodes (Group II). Of those having radical mastectomies alone 50 per cent survived 5 years clinically free from cancer, and 50 per cent died. Very few had local recurrences, but those who died must have had extension beyond the anatomic limits of surgical excision at the time of operation. Since it is impossible to be sure whether or not extension has taken place beyond the axillary lymph nodes when these are involved, it has been concluded that immediate postoperative irradiation should be given routinely. The irradiation may delay neoplastic growth and prolong life although it may not necessarily cure. The possible benefits are indicated by Group II cases of which 50 per cent of those having operations alone survived 5 years, but about 65 per cent of the patients receiving irradiation lived that long, suggesting that the treatment was beneficial.

Group III—The prognosis is less favorable for those with metastases in numerous axillary lymph nodes (Group III) than for those having few nodes involved (Group II). Two types of cases in our series of cancers of the breast were placed in Group III.

In some patients the tumors clinically appeared to be quite localized with little or no involvement of the skin and muscles, few or no palpably enlarged axillary lymph nodes and without evidence of distant metastases, but after operations and microscopic examinations metastases were found in numerous nodes. Many of these patients were obese. Undoubtedly, radical mastectomies were justified yet did

not cure. Some Group III cases had local recurrences, but distant metastases developed sooner or later in all because extension had taken place beyond the axillary lymph nodes and the anatomic limits of surgical removal. Therefore, it was concluded that postoperative irradiation should also be given to patients with metastases in any axillary lymph node.

The second type of case in this category (Group III) had unmistakable physical signs of cancer of the breast but none of distant metastases. These patients are the type about which there is the most disagreement and controversy about "operability" and "inoperability." In our experience they also were incurable; many developed local recurrences and all had distant metastases sooner or later.

These types of cases with numerous axillary nodes involved, with or without clinical evidences of incurability and without demonstrable distant metastases, constituted 30 per cent of our series. Only 5 per cent survived 5 years after operations alone, and none were free from cancer. There is statistical evidence that the average natural duration of life for women with untreated cancer of the breast is about 3 years, and 5 per cent live 5 years.[6,7] Also there is evidence that a high percentage of patients with the clinical and pathologic manifestations tabulated in Group III, when subjected to radical mastectomies do not live so long as the natural duration of life of untreated cases. This indicates that operations may shorten the lives of some patients. Therefore, it has been concluded that patients with clinical manifestations of incurability should not be subjected to radical mastectomies but should be treated by irradiation alone.

Irradiation may not cure Group III cases, but it may delay extension and prolong the lives and economic usefulness of some. Approximately 15 per cent of the patients in this category survived 5 years, although not cancer free, following operations and postoperative irradiation, whereas only 5 per cent survived as long if operations were the only treatment. It is justifiable to conclude that patients with clinical manifestations of incurable cancer of the breast will survive as long or longer than the average natural duration of life of untreated cases if no operations are performed and irradiation alone is given.

Group IV—All patients with tumors in their breasts, with or without physical signs of cancer, should be examined clinically and roentgenologically for distant metastases in lungs and bones before therapeutic procedures are instituted. Some patients with no, or even minimal, physical signs of cancer have distant metastases, although most patients with metastases will have clinical manifestations of incurability. In our series 20 per cent had distant metastases when first examined. It

is difficult to justify performing radical mastectomies upon patients with distant metastases no matter what may be the condition of the breasts. Irradiation alone should be given for palliation to the breast, regional lymph node groups, and the metastases. Irradiation of the ovaries to inhibit their function has proven to be of benefit in some cases.

Groups III and IV together included approximately 50 per cent of all cases in our series. This observation led to a study of analogous clinical and pathologic manifestations of cancer that they presented. These are tabulated in simple form as the "criteria of incurability" as follows:[6, 7, 8]

The skin

Edema ("orange" or "pig skin") of more than slight extent; ulceration of more than slight extent; brawny red and inflamed not obviously due to infection; multiple secondary nodules.

The breast

Diffuse edema; diffuse infiltration; multiple secondary tumors; fixation to chest wall.

Metastases

Axillary lymph nodes numerous, extensively involved and fixed; supraclavicular lymph nodes involved or edema of arm; distant metastases (bones, lungs, or other viscera).

Others who have studied large series of cases of cancer of the breast have found the same relative proportion of incurable cases and similar clinical and pathologic manifestations of incurability.[9, 10, 11] These criteria of incurability should be sought for, and patients with them should not be subjected to radical mastectomies but should be given irradiation for palliation and prolongation of life and economic usefulness.

It may have been noted that preoperative irradiation has not been discussed. The analysis of our series does not indicate to what types of cases this procedure is applicable.

It seems illogical to give preoperative irradiation to patients with tumors in their breasts who clinically present no manifestations of involvement of skin, muscles, or axillary lymph nodes, and no conclusive evidence of benignity or malignancy. Preoperative irradiation can be of no benefit for benign tumors and is unnecessary for cancers still localized within the anatomic limits of surgical removal. Therefore, it has been concluded that immediate operations are indicated under these circumstances (Groups I or II), with postoperative irradiation for those with metastases in the axillary lymph nodes (Group II).

On the other hand, patients with cancers of the breast that have produced clinical manifestations of incurability have extension beyond

the anatomic limits of surgical removal (Groups III and IV). No amount of irradiation that can be given by modern technics can minimize this extent of involvement nor bring it within the anatomic limits of surgical removal, although it may delay growth temporarily. In our experience, as has been reported by others, even after seemingly adequate irradiation of cancers of the breast, viable neoplastic cells remained, both in the tumor and in axillary lymph nodes although the tumors and nodes were reduced in size and some neoplastic cells destroyed. Therefore it has been concluded that since patients with the criteria of incurable cancer of the breast have extension beyond the anatomic limits of surgical removal, whether or not irradiation is given, they should not be subjected to radical mastectomies after irradiation, or at any other time, but treated by irradiation alone.

SUMMARY

1. A classification for primary cases of cancer of the breast based on both clinical and pathologic criteria is proposed for statistical reviews and as a basis for determining the indications for different methods of treatment.

2. The clinical and pathologic criteria of incurable cancer of the breast are tabulated.

3. The indications and limitations of operations and irradiation are discussed on the basis of the classification proposed and the criteria of incurable cancer of the breast.

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URETHRAL DISEASE IN WOMEN

WM. E. LOWER, M.D. and PHILIP R. ROEN, M.D.

Despite its apparent unimportance, the urethra in women is the site of many distressing ailments and is overlooked by many physicians and not infrequently by the specialist in urology as the possible site of pathologic change productive of urinary symptoms in women. It remained for such workers as Folsom[1] to call attention to the prevalence of urethral disease in women; as one speaker (Stark[2]) has stated, "I would say that the modern urologist had rediscovered the female urethra about 1930."

The diagnosis, understanding of clinical manifestations, and application of accurate therapy depend upon a knowledge of the gross and histologic anatomy and the pathologic changes involved.

The female urethra is a comparatively short tubular structure extending approximately 4 cm. from the internal urethral orifice at the bladder to the external urethral orifice in the roof of the vestibule. A cross section presents (1) a mucosal lining of squamous epithelium in its outer two-thirds and of transitional epithelium which merges with that of the trigone in its inner third; (2) this lining is thrown into longitudinal folds by a thick muscular coat which is continuous with that of the bladder. There are numerous minute urethral glands and pitlike urethral ducts which open into the lumen of the urethra. One group of these glands on each side possesses a minute common duct known as the paraurethral, or Skene's, duct, opening on either side of the external urethral orifice. The vascular layer between the muscular coat and the mucous membrane contains elastic fibers and resembles erectile tissue. Striped muscle fibers in the proximal portion of the canal form a complete ring-like sphincter, but in the middle and distal thirds, pass backwards on the outer aspect of the vagina forming a urogenital sphincter.

At the meatus and in the anterior two-thirds of the urethra, the following definite pathologic changes occur:

(1) **Congenital stenosis of the meatus.** The following case history is illustrative of this condition.

Case 1—A 2 year old child was seen at the Clinic in September, 1942 with the complaint of straining and difficulty on urination which had been noted soon after birth. Examination revealed the presence of a urethral meatal stenosis. Dilatation of the urethra up to 20 F with bougies overcame the difficulty, and the child was able to void with ease.

(2) **Urethritis.** In the acute form this is due in most instances to gonorrheal infection, though occasionally an acute inflammation may result from invasion by other cocci or the colon bacillus. Although

urethritis in men is predominantly gonorrheal, the opposite is true in women. Gonorrhea may be the cause of chronic urethral disease and stricture in women, but the relative number of cases due to this disease is very small. Chronic urethritis of nonspecific origin, on the other hand, is rather frequent. No conclusive studies of the bacteriology of female urethritis have been made; urine obtained by catheter from the bladder is often sterile; contamination from the meatus often vitiates swab or loop cultures; and, furthermore, organisms from the surface of the mucosa might not represent the true infecting agents in the deeper structures. Discharges from vaginitis, cervicitis, and puerperal infection, carelessness about vulvar hygiene and menstrual napkins, and contamination other than gonorrheal by coitus and by feces afford a varied and fertile source of urethral infection.

The symptom complex includes frequency and urgency with a stinging or burning sensation on voiding, and a constant dull pain which may be referred to the suprapubic region or the vagina. This tendency for pain resulting from chronic urethritis to be referred to other regions has often led to mistakes in diagnosis and unnecessary gynecologic operations and treatment. Terminal hematuria may also be present.

When infection occurs, particularly in the periurethral glands, drainage is retarded by swelling, and the gland structures and submucosa are invaded. The terminal picture is that of a proliferative granular urethritis. The urethra, palpated through the anterior vaginal wall, shows dense thickening, and occasionally a suburethral gland abscess may be detected.

The diagnosis of urethritis, however, should be made only by ruling out pathology of the bladder and upper urinary tract by complete urologic study. The urethroscopic findings belong in the realm of the urologist. It will suffice to say that redundant granular mucosa may be observed in the anterior two-thirds of the urethra (Fig. 1).

The majority of cases have infiltration and early contracture as their basis and respond dramatically to simple dilatation with sounds. It is a common observation that the first instrumentation, usually at cystoscopy, gives signal relief. To avoid recurrence, gradual, gentle, progressive, intermittent dilatation should be carried out. Only after dilatation up to 30 or 40 F in adults is attained, is a reasonable permanency of cure assured.

If the urethritis is permitted to continue, stricture and caruncle, or both, may supervene.

(3) **Stricture.** There is a wide divergence of opinion existing with regard to the incidence of stricture of the female urethra. This condition

Figure 1

is not quite the analogue of the annular stricture in the male, the result of chronic gonorrheal cicatrization, but is a diffuse thickening and narrowing throughout the entire length of the urethra. However, even in such diffusely infiltrated urethras more frequently there is greater stenosis at the meatus than further along the urethral canal. The symptoms of stricture are urgency, difficulty in voiding, partial incontinence, and dribbling. Treatment in this condition is again that of gradual and repeated dilatation. Rarely, incision of the stricture may be necessary.

(4) **Caruncle.** These tumors occur frequently and appear as small, red, soft masses attached to the mucous membrane of the posterior aspect of the urethral meatus. Caruncle is peculiar to the lower portion of the female urethra and does not occur in the proximal third. Caruncle manifests itself in symptoms of urgency, frequency, dysuria; often there is an exquisite tenderness to touch.

The granulomatous type of caruncle will frequently extrude and be more amenable to treatment after several dilatations. If small in amount, it may be coagulated at several points. Complete destruction is not necessary. The surface will slough, and small remaining points may be coagulated at a subsequent date. Excessive scar tissue with ensuing contracture should be avoided. Large growths are better removed by sharp dissection and the bleeding points coagulated after removal. Radium should not be used as therapy for this condition; urethral stenosis may be the aftermath of such radium treatment. Since this type of caruncle is a product of chronic inflammation, one should never be content with its removal without thorough treatment of the underlying chronic urethritis.

(5) **Suburethral abscess and diverticulum.** These conditions, while generally considered to occur but rarely, have been the subjects of numerous reports. Infection occurs in one of the suburethral glands, and with closure of the duct a small abscess results which may later rupture into the urethra and empty itself in this fashion; rupture through the vaginal wall, on the other hand, may produce a urethrovaginal urinary fistula. Repeated episodes of this abscess formation and rupture into the urethral lumen may produce a large sac communicating with the urethra, thus forming a diverticulum of the urethra. Stasis of urine in such a sac may later occasion calculus formation. Recognition

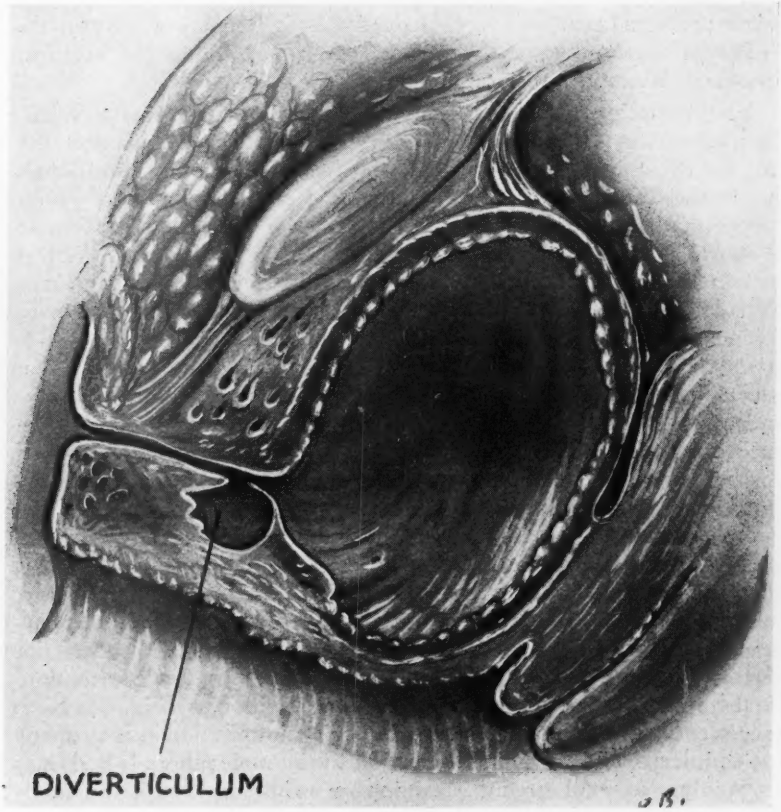

FIGURE 2

of this condition is not difficult if only it is kept in mind. A cystourethrogram with a radio-opaque solution, films being taken in the AP and oblique positions, will be diagnostic. Surgical excision of the sac is the only measure for cure. If detected in the acute abscess stage, incision will bring prompt relief (Fig. 2).

The trauma incident to childbirth with consequent weakening of the urethral wall may in certain instances also be the precursor of diverticulum of the urethra.

(6) **Neoplasm of the urethra.** Except for caruncles, true new growths of the urethra occur very rarely. Carcinoma has, however, been reported in a number of instances, and it is incumbent, therefore, upon the operator who removes proliferative lesions of the urethra to study them microscopically. Carcinoma of the urethra is an exceedingly serious problem because of the high degree of malignancy of this growth.

Polyps may on occasion be found anywhere along the urethra. Treatment is simple excision.

The posterior urethra presents a somewhat different problem. Embryologically, the posterior urethra is entodermal, whereas the anterior two-thirds are ectodermal, and the epithelium is transitional, that of the distal urethra being squamous. Recently, Beneventi[3] found true prostatic tissue and glands in the posterior urethra of the female newborn. Such a finding helps to explain the obstruction of the vesical neck in adult women, the condition simulating a true prostatic urinary obstruction of the man. It is not our purpose to argue the presence or absence of a "female prostate", but the presence of numerous glands in the posterior urethra is undisputed, and it is these glands when infected that produce very distressing bladder symptoms. The frequency, pain, urgency, and dysuria may incapacitate the individual for work or social activity. Pathologic findings are dilated vessels, polypoid or cystic degeneration at the neck of the bladder, and a corrugated, irregular, dusky outline of the internal sphincter instead of the smooth, regular, glistening, pink mucosa of the normal. Not infrequently, there is actually heaping up of tissue at the sphincter floor, with a sharp decline to the trigone. Indeed, trabeculation of the bladder wall and residual urine may accompany this finding. Folsom[1] has particularly stressed the proliferative tendency of lesions of the posterior urethra; he has described, in addition to granulations, cystic formations in the mucosa together with polypi and papillomas (Fig. 3). Such excrescences at the bladder neck produce symptoms which are exactly the counterpart of prostatic obstruction in the male: there is hesitancy on voiding, a small stream, straining on urination, and occasionally dribbling and overflow incontinence.

Treatment in these cases is not just the simple dilatation which is so effective where simple urethritis of the anterior urethra is present. The polypoid, cystic, or hyperplastic changes will require destruction by coagulation, either by topical application of silver nitrate through an appropriate cystoscope, or by the electrocautery. Occasionally, the punch or resectoscope will have to be employed to remove the obstructive tissue.

FIGURE 3

Case 2—A 53 year old housewife gave a history of difficulty in voiding of approximately 10 years' duration. There was associated frequency, nocturia, and dysuria, all of which had been steadily progressive. Cystoscopic examination revealed several papillomatous growths at the vesical neck which obstructed the urinary outflow. These were fulgurized, and the patient was much relieved of her difficulty in voiding, although some symptoms of dysuria and frequency persisted. At the time of discharge from the hospital, residual urine still measured 75 cc.

Differential Diagnosis. Symptoms of bladder dysfunction should be sought in the history of every woman patient, especially gynecological cases. Inspection of the fourchette should note the presence of vaginal discharge and the appearance of the external urethral meatus. The presence of a cystocele, atrophic vaginitis, or Trichomonas vaginalis infection should not be overlooked. A catheterized urine specimen should be obtained; the voided specimen should never be employed for examination. The bladder symptoms should not be explained away by "pressure of the uterus on the bladder." Except in the case of pregnancy or very large fibroids, such pressure is entirely physiologic and is not productive of bladder distress. Similarly, states of the urine other than infection, as polyuria from excess fluid intake or diabetes, should not be assigned etiologic significance. Too, an "acid urine" per se is never

a causative factor even though the administration of alkali may relieve frequency and dysuria to some extent. Above all, however, a thorough and complete urologic investigation should be made to discover the presence of upper urinary or midurinary tract disease before the role of causative agent is applied to the urethra. Where, however, such elimination has been done, the presence of abnormal findings in the urethra should not be minimized, and treatment should be instituted. It will often be found that the simple therapeutic measures described will frequently change a nervous uncomfortable woman with "bladder trouble" into a very grateful patient.

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HAND-SCHÜLLER-CHRISTIAN DISEASE
(Idiopathic Xanthomatosis)

Report of a Case

JOHN TUCKER, M.D.

Hand-Schüller-Christian disease occurs most frequently in children under 2 years of age. The principal manifestations of the syndrome are osseous xanthoma producing defects in the membranous bones of the skull, exophthalmos, and diabetes insipidus. The etiology is unknown, although it is generally recognized that the disturbance is related to the metabolism of lipoid material in the body. This substance accumulates in the reticulo-endothelial cells of the body either by infiltration or by some intracellular chemical change so that the affected cells are loaded with lipoid material. When this fatty substance is dissolved out and histologic study is made, the tissue cells have a vacuolated or foamy appearance (foam cells).

The clinical picture of any particular case of xanthomatosis depends upon the regions of the body invaded by these foam cells. Rowland[1] contends that many other conditions such as Niemann-Pick disease, Gaucher's disease, xanthoma multiplex, and xanthomas of the skin and tendons, with or without diabetes insipidus, are all manifestations of defective metabolism of lipoids.

The tendency for these abnormal cells to accumulate in larger or smaller tissue masses produces secondary effects in various tissues of the body. In Hand-Schüller-Christian disease the localization is chiefly in the skull. When the xanthomata involve the dura mater, infiltration and lysis of the membranous bones of the skull cause circular defects of irregular contour and replacement by a fibrous, rubbery material usually containing granulation tissue, foam cells, giant cells, and scar tissue. If these abnormal reticulo-endothelial cells accumulate about the pituitary stalk, such pathologic states as diabetes insipidus, dwarfism, pituitary cachexia, or genital hypoplasia may be observed.

Trauma or tissue inflammation may determine to some extent the localization of the xanthomatous tumors, although this is not an important predisposing factor. While the parents of the affected child often attribute the disease to a previous injury to the skull, there was no such history in our case. In many reports in the literature, hyperlipemia is an associated but not an essential finding. As in other metabolic disturbances, such as gout, the blood may show no abnormal chemical changes.

In xanthomatosis the pathologic physiology in reticulo-endothelial cells is more complex than a simple storage of excess lipoid from the fluid tissues of the body. Therefore, this disease is very probably not analogous to gout. Excellent monographs dealing with the problem of lipoid metabolism and xanthomatosis have appeared in the literature in recent years.[1,2]

In our case, 2 of the 3 criteria for a diagnosis of Hand-Schüller-Christian disease are met: defects in the membranous bones of the skull and diabetes insipidus. Clinical and pathologic study ruled out nonspecific osteomyelitis, sarcoma, Tay-Sachs disease, Niemann-Pick disease, and Gaucher's disease. Likewise, the gratifying response to deep x-ray therapy and injections of pituitrin corresponds to the experience of many others who have treated this condition.

Obviously, the operation performed upon the left mastoid when the patient was 2 years of age was the result of a mistake in diagnosis. Cases of Hand-Schüller-Christian disease associated with discharging ears have been reported by Rowland, Schüller, Hand, and Gross and Stiffel. The possibility of xanthomatosis should be considered in atypical cases of apparent otitis media and mastoiditis even though it is an uncommon disease.

CASE REPORT

A girl, aged 2½ years and an only child, was admitted to the Clinic on January 10, 1942 with the chief complaints of marked thirst and polyuria. A foul discharge from behind the left ear and in the left parietal area caused considerable concern.

Her birth had been normal. She had been breast-fed for 2 months and then had been given evaporated milk feedings with adequate vitamins and minerals. When 3 months old she had developed discharging ears. This had continued until 2 years of age when a left mastoid operation had been performed which had failed to heal. A continuous, foul-smelling discharge had persisted in spite of local treatments. At this time a similar sinus had appeared in the left parietal area, and a softened area of bone had been noted in this region.

Marked thirst and polyuria had developed suddenly and simultaneously. The child was almost constantly at the water spigot demanding a drink, and the mother estimated that she consumed well in excess of 2 gallons of fluid a day. She was able to sleep from 8 in the evening to 6 in the morning without fluids, although she always awakened with extreme thirst. A corresponding polyuria caused her to soak the bed thoroughly each night.

The child's disposition suffered considerably with general restlessness, irritability, and an unwillingness to play with other children. Her appetite was poor, she lost weight, and her skin became dry. There was no pain and no complaint save thirst and polyuria. The patient had escaped all of the usual diseases of childhood except an occasional mild head cold.

Physical Examination

The patient was of normal height for her age, but her general nutrition was poor. The skin was rather pale and quite dry. The abdomen was protuberant, but there were no signs of rickets. There were no generalized skin eruptions. The scalp showed seborrheic dermatitis, and discharging sinuses were found in the left parietal and left mastoid regions. These areas were crusted, and a foul odor was present. A soft pulsating defect could be seen in the left parietal bone. The edges were firm and sharp. Similar defects could be felt in the occipital and left mastoid areas.

The face was round and pale; the tongue and throat dry; and teeth normal. There was no sponginess nor bleeding of the gums. The eyes showed no exophthalmos; the pupils reacted to light; and the optic discs were flat. The scleras were clear. The heart, lungs, and extremities were normal. While the abdomen was protuberant, there was no clinical evidence of ascites, tumor masses, nor any enlargement of the liver or spleen.

Laboratory Findings

Urine: specific gravity—1.000; Ph—6.5; albumin—0; sugar—0; microscopic examination—normal

Blood sugar—99 mg. per cent (fasting)

Blood chlorides—561 mg. per cent

Blood cholesterol—176 mg. per cent

Blood Wassermann—0-0-0; Kahn—negative

Blood counts: red blood cells—4,890,000 per. cu. mm.; white blood cells—6500; hemoglobin—68 per cent (Haden-Hauser)

X-ray of Skull

A biopsy of the skull in parietal area showed complete lysis of bone. Underneath this softened area the dura was exposed, and was thick and covered with a mass of granulation tissue.

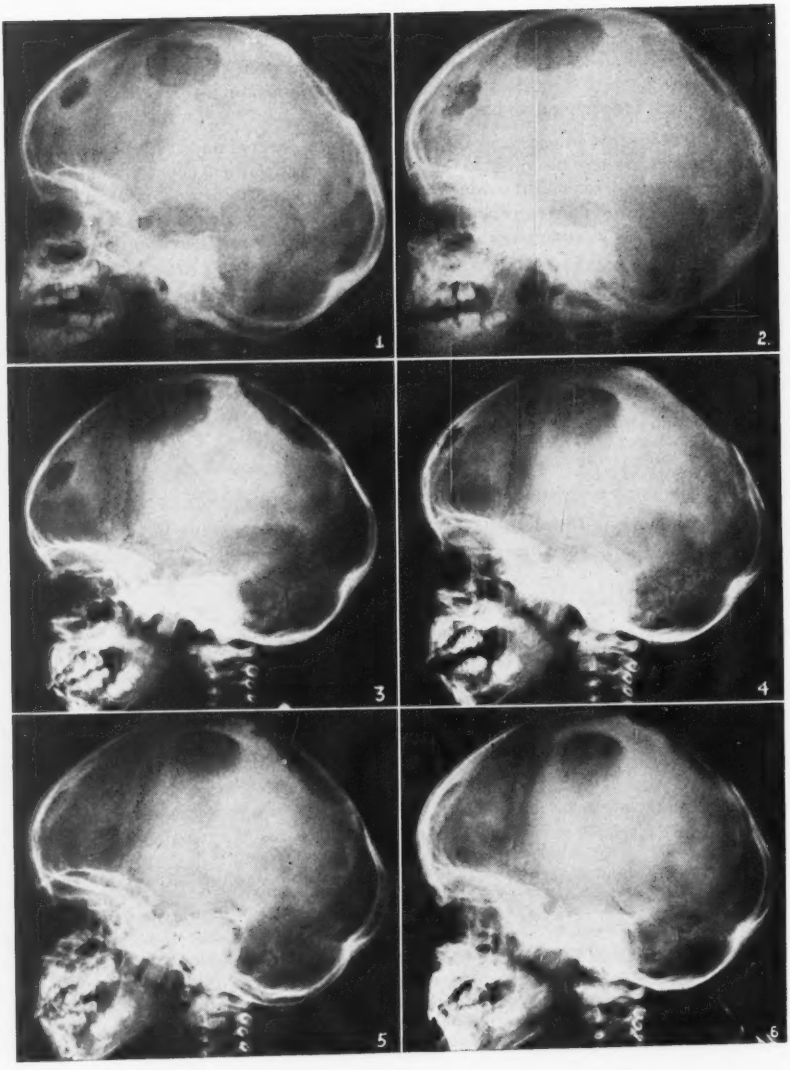
The histologic appearance showed much fibrous and granulation tissue. The marrow spaces in the bits of bone showed pink-staining, intercellular substance. Numerous giant cells were observed, but no stainable lipoid material could be seen.

Treatment

Adequate amounts of fluid were placed at the disposal of the patient. The diet was well balanced and simple without restriction of fat.

Pituitary extract was administered hypodermically beginning with 3 min. 3 times daily and increased gradually to 1 cc. 3 times daily. This drug was well tolerated, and the fluid intake fell to 1 quart in 24 hours when the full dose of pituitrin was given. The medication was then changed to pitressin tannate beginning with ½ cc. daily, followed by 1 cc. every 2 days. This drug, which is absorbed slowly, prevented the excessive thirst fully as well as the previous medication.

After the diabetes insipidus was under control, x-ray therapy was given to the involved areas of the skull. The first course was administered daily except Sunday from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X-ray Studies

The x-rays of the skull shown in Figures 1 and 2 were taken prior to the patient's admission to the Clinic.

Figure 1. Multiple bony defects involve the temporal, occipital, parietal, and frontal areas.

Figure 2. Taken 4 months later shows an increase in size of all of the lesions. The borders are moth-eaten in appearance.

Figure 3. Represents the first x-ray film taken at the Clinic. There is further advance in the lysis of bone with a new defect of small size appearing in the parietal region.

At this time x-ray therapy to the skull was begun.

Figure 4. This picture shows considerable bony repair in all of the affected areas with the possible exception of the occipital defect.

Figure 5. There appears to be complete healing of the areas behind the left ear as well as the smaller lesions in the left parietal bone and the frontal bone.

Figure 6. Further improvement in bone deposit is shown in all the remaining defects.

July 25 to August 8, 1942. A second series of radiation treatments was given from April 7 to April 14, 1943.

Results of Treatment

The most striking effects were shown not only in the satisfactory control of thirst but also in the marked physical and mental improvement. The patient has been able to eat and sleep well. She is cheerful and now plays normally with other children.

An examination on June 4, 1943 showed no physical abnormality except for a visible pulsation in the parietal area of the skull. The scalp, while hairless over the calvarium, showed no eczema, and the sinuses had healed. The skin was of normal texture and showed a normal quantity of subcutaneous fat.

At the present time she drinks about 2 pints of fluid in 24 hours and requires the injection of 1 cc. of pitressin tannate only twice a week. Evidently the diabetes insipidus has not been cured since her thirst increases somewhat as the time for her semi-weekly injection approaches. To date, fat in her diet has not been restricted, nor has she been given thyroid extract or any other type of medication.

The diagnosis of this case meets the requirements of Hand-Schüller-Christian syndrome. With the use of x-ray therapy, the correction of the bony defects has been satisfactory. The parents are delighted with the results to date, but they understand that further x-ray therapy and a longer use of pitressin tannate will be required. If the disease cannot be cured by x-ray therapy, we hope to arrest its progress until puberty, since the prospects of recovery are much better after that age has been reached.

SUMMARY

1. A case of Hand-Schüller-Christian syndrome is presented.
2. X-ray therapy has caused extensive healing of the bony defects.
3. The use of pitressin tannate has simplified the treatment of the diabetes insipidus by requiring the use of only 1 cc. twice a week.
4. The patient appears to be normal in her growth, nutrition, and mental reaction.

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GASTRIC CARCINOMA AND THE MUCOSAL RELIEF TECHNIC

FREDERIC E. TEMPLETON, M.D.

It is the purpose of this article to outline briefly some of the newer concepts in the roentgenologic examination of the gastrointestinal tract, and to illustrate their application in the diagnosis of gastric carcinoma. The roentgenologic images obtained by these newer technics differ considerably from those obtained by the older method; the amount of useful information gleaned by using the newer technical process depends upon the examiner's ability to apply that method and interpret the results.

In the early days of roentgenology the gastrointestinal tract was examined either by studying a series of films exposed with the patient in various positions or by fluoroscopic observations after filling the organ with an opaque mixture. Attempts to devise a procedure retaining the advantages, but eliminating the disadvantages, of each method led to the development of a special instrument, "the filming fluoroscope."

The filming fluoroscope, as its name implies, is an instrument designed not only for the fluoroscopic examination of a patient but also for the exposing of films under fluoroscopic control. The instrument is sometimes called the "spot fluoroscope," because in some of the commercial varieties the exposed portion of the film is small and circular. For nearly a quarter of a century Forssell, Ackerland, Berg, Chaoul, and numerous other European authors have been writing about the instrument, the special technics developed for its use, and the interpretation of the fluoroscopic and film images. Until recently, most American radiologists have looked upon films as relatively unimportant adjuncts to the fluoroscopy. This attitude changed rapidly, however, with the introduction of the first commercial American filming fluoroscope in 1934.

The newer method of examining the gastrointestinal tract differs from the old, not merely in the greatly increased emphasis on films but also in the details of fluoroscopy itself. Ideally, the aim might be to examine every square inch of the image cast by the mucosa of the alimentary tract on the fluoroscopic screen and to record on films every area observed. Actually, of course, limitations of time and expense, and above all the safety of the patient and examiner reduce the extent to which this ideal can be realized, and not infrequently the body build of

the patient curtails the completeness of the examination regardless of the amount of radiation that the examiner is willing to tolerate.

Frequently, films provide objective confirmation of lesions suspected that were not observed at all during fluoroscopy. The desire to obtain good films spurs the examiner to a more careful and a more complete fluoroscopic examination. On the other hand, vague but repeated fluoroscopic evidence may lead to persistent filming that eventually is rewarded by the demonstration of a small, but nonetheless important, lesion.

Certain terms are best defined at the outset. When the patient ingests a small amount of contrast medium, such as a mixture of equal volumes of water and barium sulfate, and when this contrast material is spread in a thin layer over the mucosa of the organ being examined, one sees on the fluoroscopic screen a mucosal pattern in which the ridges, folds, nodules, and other elevations are bright and the barium caught in the interfold spaces is dark. On films the pattern is reversed, the elevations being black and the interfold spaces white. In both cases since the appearance is somewhat similar to a bas-relief in which the elevations stand out against the background of interfold spaces, the technic of obtaining such fluoroscopic images or films is termed the "relief technic."

Sometimes the mucosal pattern is demonstrated to better advantage by employing what is known as the "compression technic." More barium is administered, balsa-wood blocks, rubber bags, or pads of gauze and cotton are inserted between fluoroscopic screen and patient; a self-locking mechanism on the screen is brought into play; and the screen is pressed against the abdomen of the patient until the desired degree of compression is obtained. Finally, the older method, the so-called "filled organ technic," is employed. As its name implies, this is merely the examination of the organ after it has been completely filled with contrast medium.

By combining the old method and the new, diagnostic criteria become more precise. As the images obtained more nearly approximate those seen at gross pathologic examination, the roentgenologist begins to think in pathologic terms, and such words as "niche," "filling defect," and "incisura" give way to "ulcer crater," "polypoid mass encroaching on the lumen," and "scar tissue contraction."

Identification of Gastric Carcinoma

In discussing the gross pathology of gastric carcinomata, seen by using the relief and compression technics, the classification of Borrmann,

as modified by Konjetzny is chosen. Descriptions are limited to the "average" appearance. The merging of one type with another frequently makes it difficult to classify accurately a given lesion. The classification consists of four large groups.

1. Localized polypoid tumors
2. Localized ulcerating carcinomata
3. Ulcerating carcinomata with invasion of the surrounding tissues (transition type)
4. Diffuse infiltrating form
   (a) Fibrosing
   (b) Polypoid

The **rare, localized, polypoid** tumor seen at roentgenologic examination is usually broad-based, sometimes pedunculated. It protrudes into the lumen as a rough plateau, or ball-like, nodular mass with a smooth or uneven surface resulting from warty granulations, ulcerations, and fissures arising from disintegration of tissue (Fig. 1A). If the ulceration is marked and involves most of the tumor, a dishlike excavation with high margins results. In this state it has the characteristics of

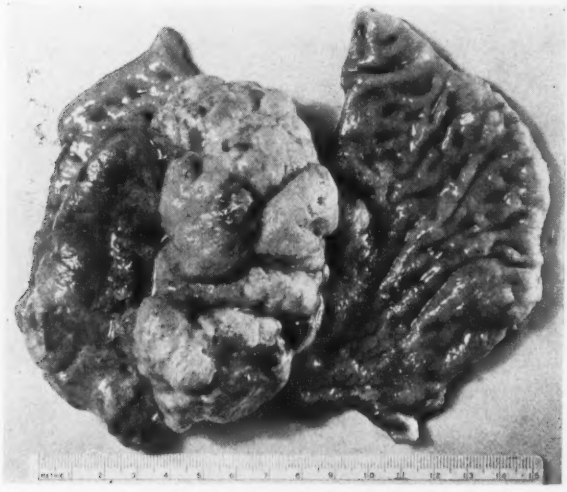


FIGURE 1. **Polypoid carcinoma.** (a) Gross specimen. Deep fissures and ulcerations separate the polypoid elevations.

the localized, ulcerating type. The hook shape of the stomach is often preserved, and the appearance of the defect depends upon whether it is seen in the frontal or profile projection. In the frontal projection the defect may be large enough to fill, or even expand, the lumen (Fig. 1B). The surrounding mucosa is pliable, and the rugae appear normal or "cut off" sharply at the tumor margin. Although this "cut off" of folds is theoretically sound in establishing the malignant nature of the lesion, the sign may be misleading. Too much compression over the lesion may

FIGURE 1. **Polypoid carcinoma.** (b) A large polypoid carcinoma fills the lumen of the midportion of the stomach. Angular dense shadows, representing barium puddled in ulcerations and fissures, outline the polypoid elevations.

A FIGURE 2 B

A large polypoid lesion invading the pancreas was found high on the posterior wall at operation. (a) In the filled stomach a small polypoid defect appears near the lesser curvature. Most of the tumor is covered with barium. (b) With relief films the entire tumor is outlined. Some of the folds on the anterior wall are superimposed on the shadow of the tumor.

completely obliterate all of the folds. This is particularly true in the antrum if too much barium is used. Folds on the opposite wall may also be obliterated by pressing against the tumor mass which produces a false appearance of "cutting off" of folds. If too little pressure is used, the rugal pattern of the opposite wall may be preserved, in which case folds seem to run through the tumor (Fig. 2). In the profile views barium flowing around a tumor located on a curvature may produce an hour-glass-like deformity of the stomach.

The **circumscribed ulcerating** carcinoma is common. Carmen described three different appearances produced by approximating the walls of the stomach: (1) A crater on the vertical portion of the lesser curvature produces a crescentic or meniscus-like shadow, the convexity of the crescent toward the gastric wall and the concavity toward the

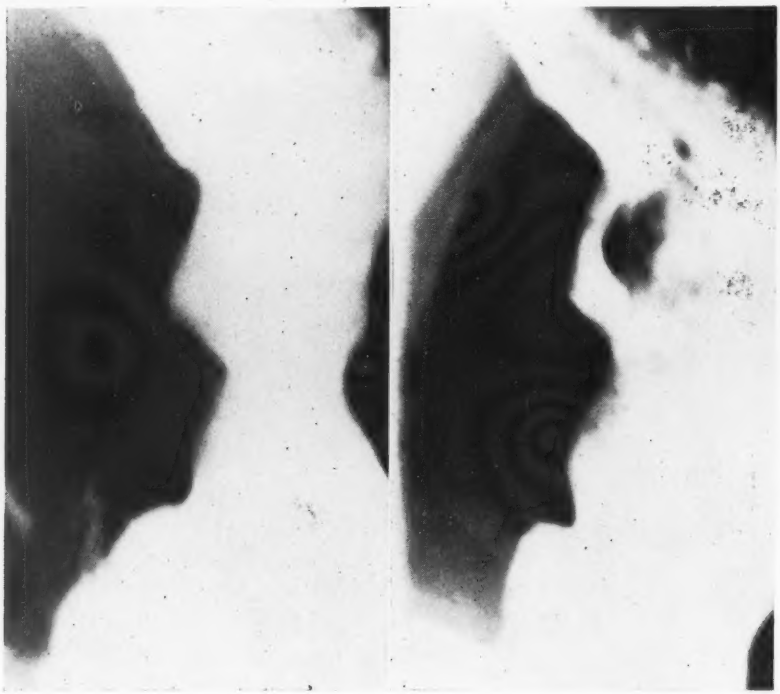


FIGURE 3. **Ulcerating carcinoma.** (a) A crater filled with barium protrudes from the lesser curvature of the body. (b) With compression excess barium has been displaced. The base of the crater is outlined by a meniscus-like shadow whose concavity is directed toward the gastric lumen.

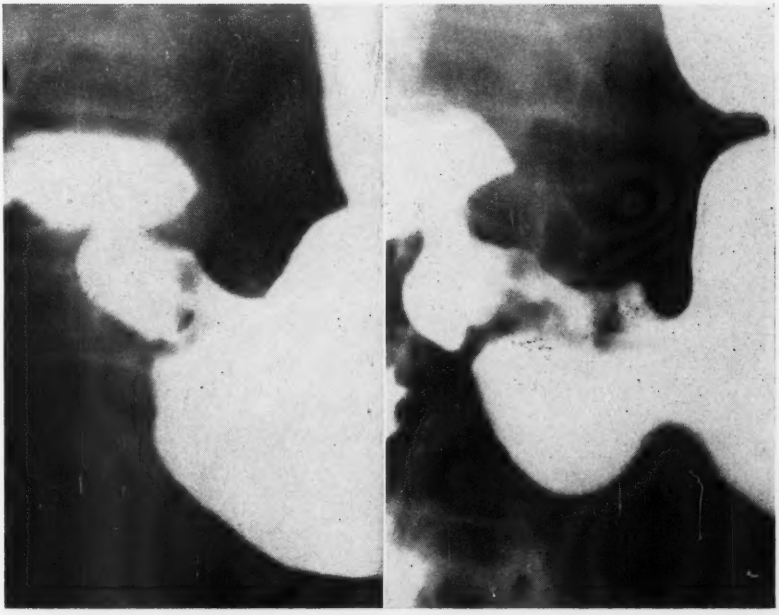
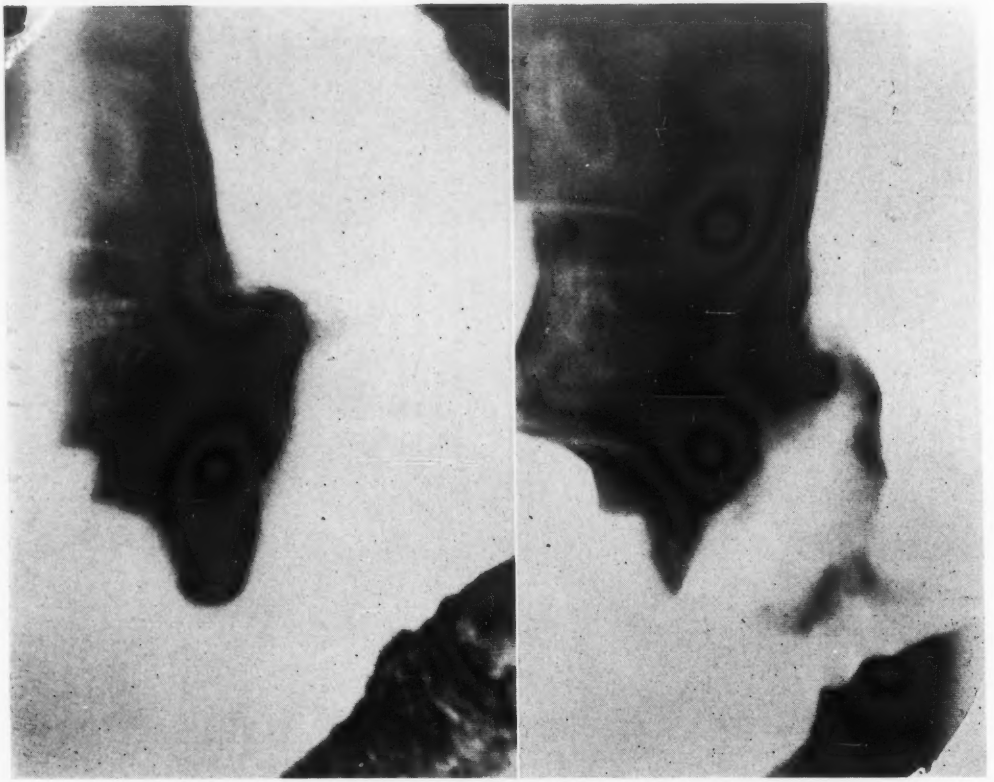


FIGURE 4. **Ulcerating carcinoma.** (a) With the stomach filled with barium, a section of the lesser curvature of the antrum is concave. (b) With compression the concave margin of the lesser curvature proves to be the base of the crater. The crater is set-off from the rest of the barium in the stomach by an irregular halo which represents the rolled-up margin about the crater.

lumen. (2) A saddle ulcer distal to the angle of a fishhook type of stomach also appears as a meniscus, but in this instance the base of the ulcer follows the bending line of the curvature, and the concavity of the meniscus is toward the gastric wall. (3) An ulcer distant from either curvature on the posterior wall appears as a circular crater surrounded by a halo and in oblique or profile views does not protrude beyond the contours of the stomach.

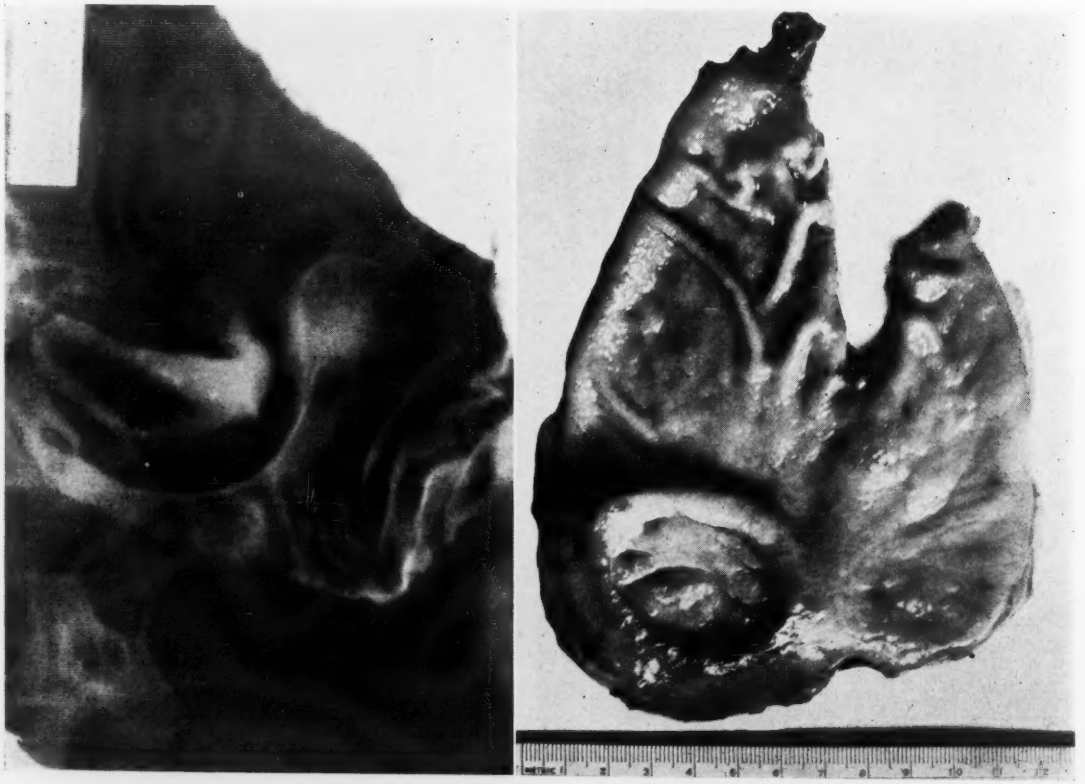
A carcinomatous ulcer with an appearance as described by Carmen in the first group is rare (Fig. 3). A lesion similar in appearance to that described in the second group on the vertical portion and at the angle of the lesser curvature is occasionally encountered (Fig. 4). If one wall of the ulcer is seen in a true tangential projection along the lesser curvature of a barium-filled stomach, an elongated depression results (Gutmann). The upper and lower margins of the lesion are sharp. Occasionally, the normal mucosa "mushrooms" over the rolled-up margin,



A FIGURE 5 B

Ulcerating carcinoma. (a) The elongated depression with its sharp superior margin represents one wall of an ulcer crater seen tangentially. (b) With compression an irregular crater set-off by a rolled margin is evident.

an ulcer crater seen tangentially. (b) With compression an irregular crater set-off by a rolled margin is evident.



A FIGURE 6 B

Ulcerating carcinoma. (a) A large crater, with polypoid masses in the base outlined by barium, is surrounded by a high rolled margin. (b) Gross specimen.

giving the appearance of a small crater, and the actual tumor is overlooked. This can happen either at fluoroscopy or during the making of a film if the examination is done on a filled stomach without the use of compression. By approximating the anterior and posterior walls of the stomach by pressure, the barium in the crater which lies within the gastric margin is set off from the mass of barium in the stomach by the rolled, often irregular, margin of the ulceration (Fig. 5).

The ulcerating carcinoma described by Carmen in the third group is similar to that of the second group except that the crater is seen in the frontal projection. The margin of this ulcer may be smooth and circular but is frequently angular, irregular, and jagged. Sometimes, by severe compression, prominent polypoid elevations can be identified in the base (Fig. 6). As in the case of craters seen in profile, irregularity of the margin is caused by the polypoid nature of the elevated wall. The appearance of the rugae surrounding the lesion and on the opposite wall is similar to that encountered in the localized polypoid types.

In the pylorus the ulcerating tumor may spread in a ringlike form, causing stenosis (Klein). In the filled stomach this results in a stiff, ragged, narrowed lumen. If compression is used, the proximal edge of the sharply defined, rolled-up margin can be identified. The distal margin can seldom be outlined, as the lesion extends down to the pyloric canal, or sufficient barium cannot be forced beyond this margin to outline it (Fig. 7).

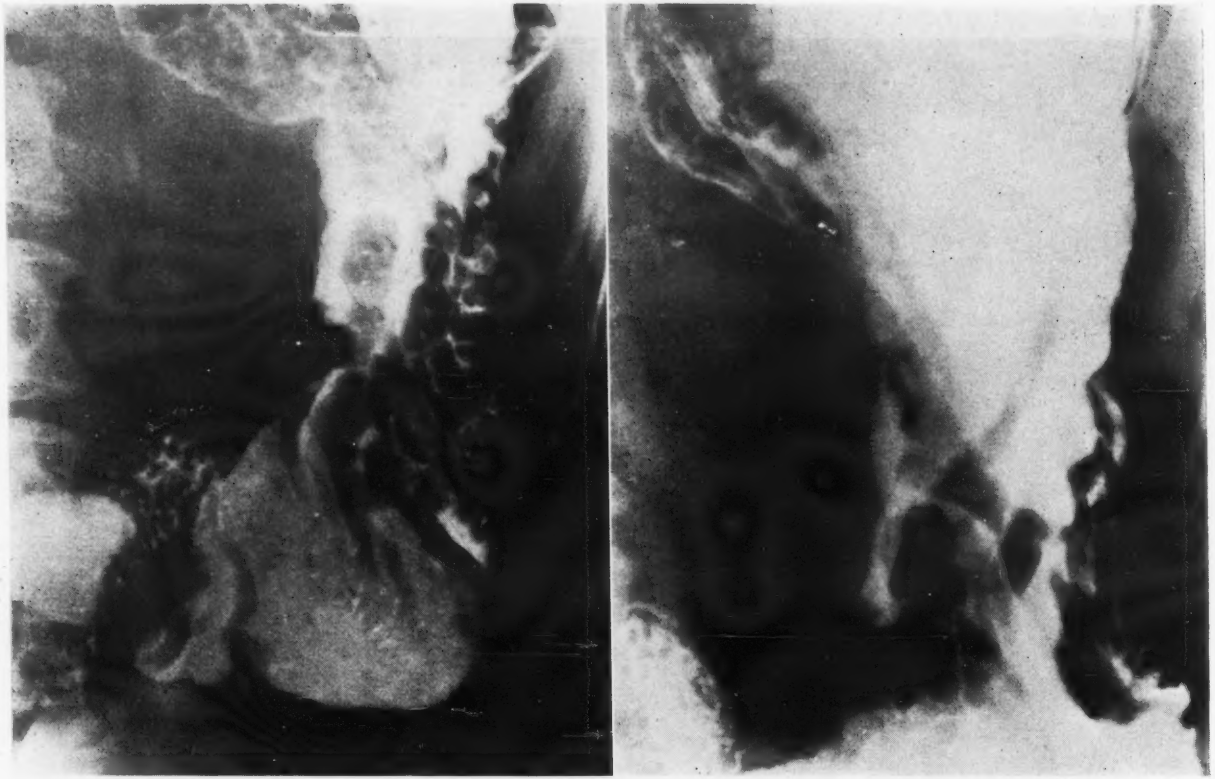
Berg pointed out that small tumors in the pylorus may be overlooked if the rolled margin has the same direction as the normal folds, as the margin may be easily confused with benign swelling. This is possible if one depends upon the results of the examination after a single swallow of barium, but is not so likely if compression is used on the filled stomach. Compression causes the crater to fill, whereas the former method may not. The failure of a crater to fill when too little barium is used with the hope of obtaining better relief views must always be kept in mind.

If the ulcer erodes beyond the level of the gastric wall, a pocket is produced which protrudes beyond the line of the curvature. The gastric wall falls sharply away from the ulcer margin, giving evidence of sharp demarcation which is a factor used in differentiating these lesions from the next type.

The **infiltrating carcinomatous ulcer of transition type** is, according to Berg, the carcinoma most frequently confused with benign ulcer, especially in the early stages, as it has a definite crater and may be associated with radiating folds. It may appear similar to the localized form except that part or all of the elevated margin is not so high, and consequently the adjacent gastric wall does not fall sharply away. This grad-

A FIGURE 7 B

Ringlike carcinomatous ulcer of the antrum. (a) The ragged contours of the antrum were produced by neoplastic infiltration. (b) With compression normal rugae stop abruptly at the proximal rolled-up margin of the ragged crater encircling the antrum.



A FIGURE 8 B

Flat, ulcerating, infiltrating carcinoma of the lesser curvature, proved to be inoperable. (a) The lower margin of the long, shallow ulcer set-off by a wide polypoid ridge is sharply defined. The upper margin fuses with the adjacent gastric margin. (b) Compression exerted over the lower margin of the crater brings out radiating folds and polypoid lesions in mucosa below the level of the crater.

ual merging of the infiltrated wall with the surrounding structures is evidence of infiltration beyond the confines of ulceration. If the lesion is situated along, or close to, the lesser curvature, which it frequently is, evidence of infiltration is usually seen first along the oral portion of the tumor. The surrounding mucosa may be involved by neoplasm or hyperplastic gastritis of a degree severe enough to produce roentgenographic changes. The folds are broad, stiff, and prominent, or the normal pattern is replaced with small, warty, mucosal thickening to nodular, polypoid growths of different sizes. The actual extent of the malignant changes cannot be estimated, and the gastritis cannot be differentiated from carcinoma, either at gastroscopic or at roentgenologic examination (Schindler). This appearance may be confused with that of the diffuse infiltrating carcinomata, particularly of the polypoid type (Fig. 8).

The **infiltrating carcinoma,** particularly the localized, nonulcerating, fibrosing type, offers the greatest diagnostic difficulty in that it may easily escape detection (Eisler). If the mucosa is not fixed and the tumor is soft, it may be impossible to identify the lesion. The pattern of the folds may not be appreciably changed, and peristalsis may pass through the lesion, as reported by Kirklin, a phenomenon I have also observed.

If a small portion of one curvature is fixed, the only evidences of infiltration may be a slight straightening of the curvature (Cole), protrusion of the normal mucosa over the proximal edge of the lesion giving the appearance of a small crater, and the "peristaltic jump" of Fränkel. In this latter sign the peristaltic wave progresses in an uninterrupted manner along the uninvolved curvature opposite the tumor, but ceases at the proximal edge of the tumor only to reappear at the distal edge (Fig. 9).

If the infiltration is advanced, the pattern of the normal folds is obliterated, or is replaced by stiff irregular folds with narrow interspaces.* The line of demarcation is not sharp, the normal folds gradually losing their identity in the abnormal patterns.

*Loss of fold pattern in the antrum may be physiologic as well as pathologic. After a small swallow of barium various types of fold patterns appear in the antrum. If the stomach is filled with barium and compressed, no folds may be seen; if the patient is placed supine after taking the barium, the air which gravitates to the antrum and results in a "double contrast view" may distend the antrum sufficiently to obliterate folds. This observation is in keeping with the findings of the gastroscopist, who rarely sees antral folds. The smooth mucosal pattern does not necessarily indicate the presence of atrophic gastritis, which is easily differentiated from neoplasm by the presence of the folds in the collapsed antrum as seen after a single swallow of barium, by its distensibility by air in the stomach, and by pliability to external manipulation and passage of peristaltic waves.

shallow ulcer set on by a wide polypoid ridge is sharply defined. The upper margin fuses with the adjacent gastric margin. (b) Compression exerted over the lower margin of the crater brings out radiating folds and polypoid lesions in mucosa below the level of the crater.

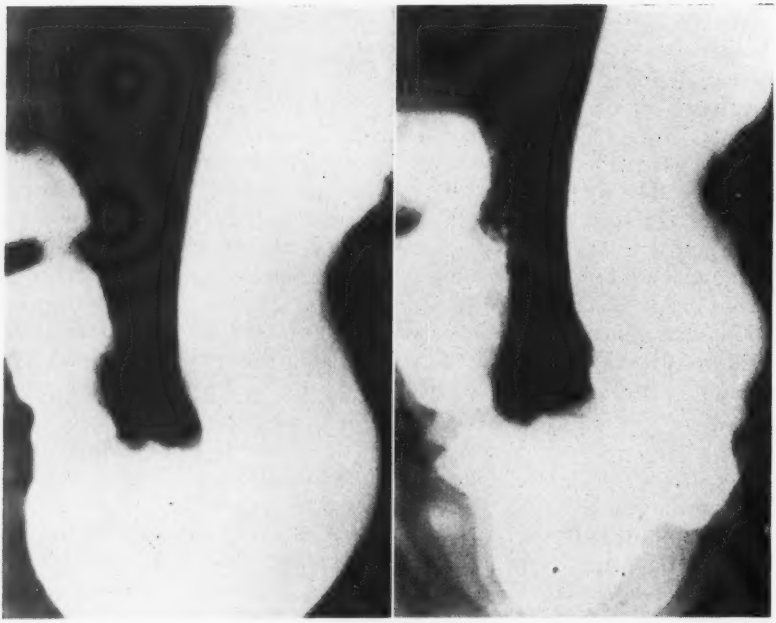


FIGURE 9. **Small infiltrating carcinoma.** (a) In the filled stomach the lesser curvature of the antrum is irregular. (b) Polygram. This view was made by giving ⅓ the normal exposure three times at intervals of 2 seconds. The progressive peristaltic waves can be identified along the greater curvature and the lesser curvature of the body. The infiltrated portion indicated in (a) is not affected by peristalsis.

If both curvatures are involved, they are abnormally smooth and straight.

In the far advanced case in which the entire stomach is involved, the diagnosis is more easily made by filling the stomach completely. The small, stiffened, foldless lumen with its pipelike passage of barium is characteristic (Fig. 10).

The polypoid type appears similar to the fibrosing type except that the nodular ulcerated mucosa results in various translucent rounded areas of various sizes (Fig. 11). The involved region is stiff, so that the pattern cannot be changed by variations in pressure during palpation. There is no sharp demarcation between the normal and the abnormal

pattern. This type rarely involves the entire stomach and cannot always be differentiated from the fibrosing type by the roentgenologic observation if ulceration is pronounced.

Both types, if confined mainly to the antrum, result in a tubelike, or funnel-shaped, canal from contraction of the fibrous tissue. This may either cause obstruction or hold the pylorus open, allowing rapid emptying. If the lesion is confined to the center of the stomach, an hourglass-like deformity may result. This is particularly true of the fibrosing type.

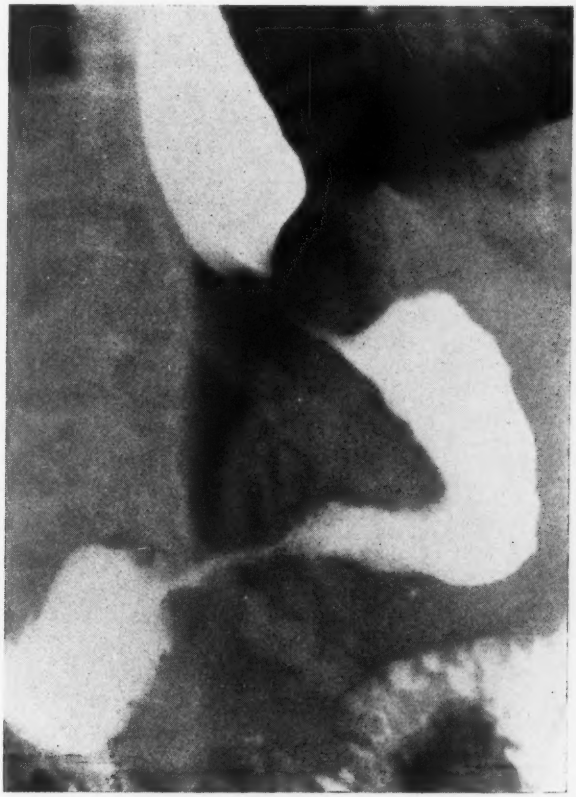
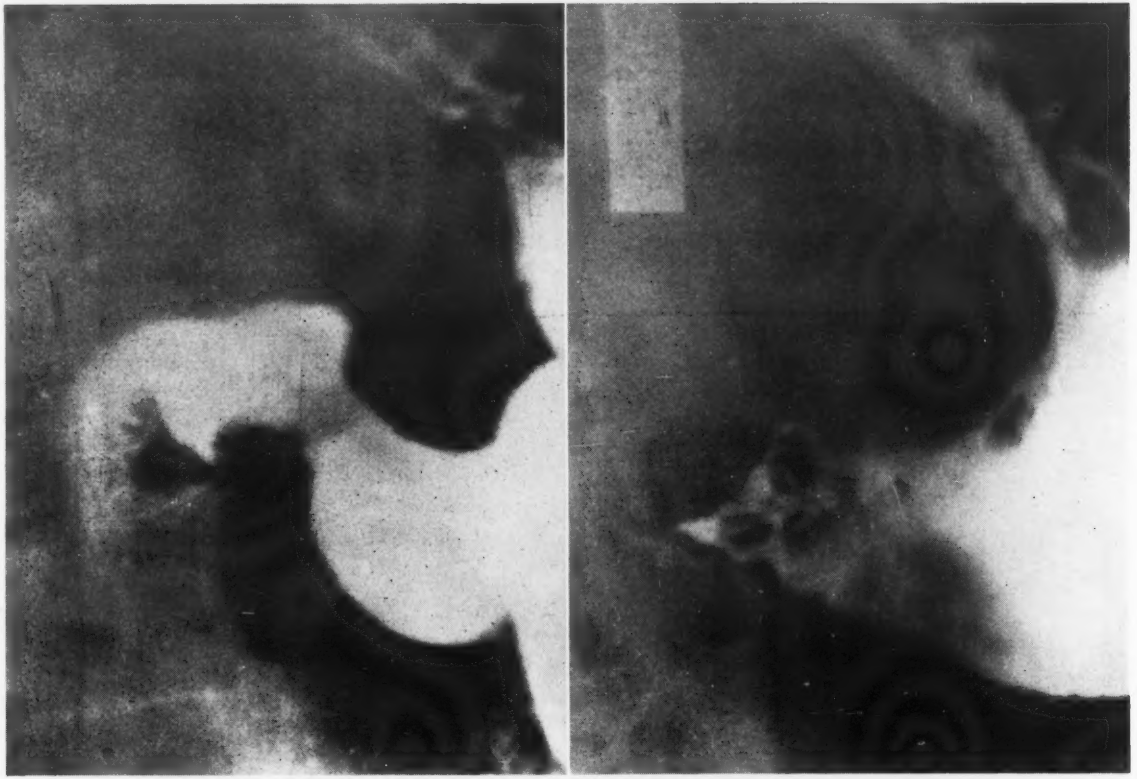


FIGURE 10. A diffuse, infiltrating, fibrosing carcinoma has involved the entire stomach and lower end of the esophagus.



A FIGURE 11 B

Small, infiltrating, polypoid carcinoma of the antrum. (a) Filled stomach. (b) After application of pressure. At subtotal gastrectomy the three polypoid elevations indicated in the reproduction were observed in an infiltrating carcinoma which extended down to the pyloric canal.

An infiltrating lesion in the fundus is particularly difficult to identify as the rib margin interferes with adequate palpation. Polypoid masses cause the stream to split into two or more components as it enters the stomach. The relief methods give valuable aid, as overdistension of the fundus with barium covers up a lesion involving either the posterior or anterior wall (Kirklin). One must beware of placing too much emphasis on the increase in distance between the fundus and diaphragm as a diagnostic sign provided that the dome of the fundus fills out smoothly and appears pliable to changes in the position of the diaphragm or transmitted pulsation from the heart. In the partially distended fundus folds running over the dome, seen on the axial projection, give a more or less regular serration similar to that seen along the greater curvature. Frequently, the observation of carcinomatous masses against the gastric air bubble may be facilitated by partially filling the stomach with barium with the patient supine. By turning him to a prone or upright position, the bulk of the barium falls away, sometimes leaving a film of barium on the surface, sharply outlining the lesion against the air. Such patterns may be more pronounced if the distention is not too great. Greater distention may roll the lesion around to either the anterior or the posterior wall so that the shadows are less pronounced or lost when seen in the anteroposterior projection. Here again the examiner must beware, for at times a normal, slightly distended fundus, insufficiently coated with barium, may give irregular shadows not unlike carcinomatous masses. In all cases careful examination of the lower end of the esophagus is necessary to determine the presence or absence of infiltration as these lesions frequently involve this region.

Differential Diagnosis of Gastric Carcinoma

In some localized polypoid types of carcinomata, the appearance leaves little doubt as to the malignant nature, but in other types differentiation from a benign lesion is at best only a guess. If the lesion fulfils the criteria described earlier, especially if the lobulations, fissures, and ulcerations are found, it is surely malignant. If the surface is smooth, if there is no infiltration of the neighboring mucosa, or if folds encircle the tumor to enclose it, it is usually benign. In such a case, however, it is not possible to determine the absence or presence of malignant cells in the polyp if the mucosa is not involved. Fortunately, polypi and localized polypoid carcinomata are rare, so that this problem of differentiation does not occur frequently.

Palmer, in discussing ulcerating gastric lesions, concluded that (1) the existence of carcinomatous degeneration in benign ulcer remains to

reproduction were observed in an infiltrating carcinoma which extended down to the pyloric canal.

be proved conclusively; (2) peptic ulceration of carcinoma may produce a lesion grossly indistinguishable from benign ulcer; and (3) although there is no pathognomonic sign to indicate the benign nature of the lesion, the total evidence available from careful roentgenologic, gastroscopic, and clinical studies permits differentiation of benign and malignant gastric ulcer with a high degree of accuracy.

There are, however, certain types of ulcerating lesions which leave very little doubt as to their benign or malignant nature when first seen at roentgenologic examination. The protruding ulcer, whose crater margin is rounded and regular and sharply undermined, and which is set off from pliable normal-appearing mucosa, either with or without a few radiating folds, by a smooth rolled-up margin, is usually benign. The ulcer fulfilling the criteria of Carmen by presenting the meniscus-like complex is surely malignant. If the ulcer simulates the appearance of the infiltrating, transition type of ulcer or is large, differentiation between a benign and malignant lesion may not be made from roentgenologic evidence alone. The hypertrophic changes in the gastritis, which sometimes simulates a benign ulcer, may appear similar to the neoplastic infiltration about this form of carcinomatous ulcer. In these cases a period of medical management may be instituted, since the rapid diminution in size and eventual disappearance of a crater as seen at either gastroscopic or roentgenologic examination is an important factor in establishing the benign nature of an ulcer.

In evaluating this evidence, the ulcer must not only disappear but must leave soft, pliable mucosa, through which peristalsis passes at the former site of the crater. The crater of an ulcerating malignancy occurring in a stomach producing free acid will fill in with neoplastic tissue. The crater disappears but the infiltration remains. The stiffness which this infiltration produces can be detected (Fig. 12). Bloomfield has justified the delay in diagnosis by pointing out that the incidence in error in the clinical differentiation is not greater than the mortality rate from a sub-total gastrectomy.

Some infiltrating carcinomata may not be differentiated from the rare forms of hyperplastic gastritis, either at gastroscopy or roentgen examination. Templeton and Schindler point out that the passage of deep peristaltic waves through the stomach is helpful in differentiating certain forms of gastritis from carcinoma. Also, they presented a case of polypoid gastritis in which multiple polyp-like lesions were scattered throughout the antrum. Following the lead of Berg, they stated that this finding is apparently the only sure sign of gastritis. In view of Konjetzny's work suggesting that these forms of gastritis may become carcinomatous,

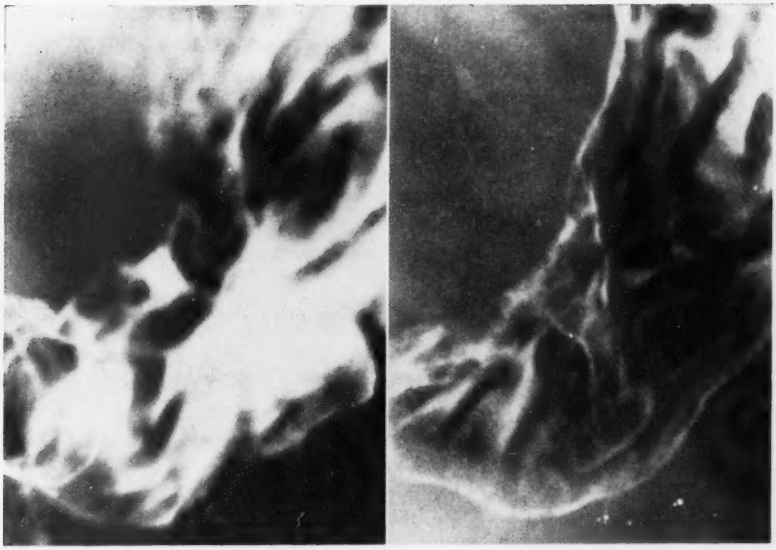


FIGURE 12. **Carcinomatous ulcer disappearing under medical management.** (a) An irregular crater having poorly defined margins is present along the lesser curvature of the antrum. Free acid was present in the gastric juice. (b) On medical management the crater disappeared but an area of infiltration remained. The stiffened area was difficult to identify at fluoroscopy, but peristalsis failed to pass through the region. (See Fig. 9)

it now seems reasonable to suppose that the criteria are not absolute. Berg has also stated that if a stiffly infiltrated stomach with large rugae is accompanied by a demonstrable crater or stiff polypoid folds in the duodenum, the gastric lesion is inflammatory.

SUMMARY

1. The advantages of using the filming-fluoroscope (spot machine) in gastrointestinal diagnosis are briefly discussed.

2. The use of the filming-fluoroscope and the interpretation of the images obtained by it in gastric carcinoma including some of the problems of differential diagnosis of gastric carcinoma are outlined.

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DIAGNOSIS AND TREATMENT OF UNUSUAL PARIETAL PAIN

Report of a Case

CHARLES C. HARTSOCK, M.D.

The purpose of reporting this interesting case is to call attention to a very simple but exceedingly valuable procedure as an aid in the diagnosis and treatment of some puzzling types of parietal pain. Because of their curious nature such pains are often confused with deep seated visceral pain. As a result of such confusion extensive diagnostic and more extensive therapeutic procedures are used in attempting to find the source of the elusive pain when much simpler measures will suffice if applied first.

My interest in this method was aroused about a year ago when I was asked to see an Italian laborer who had been incapacitated for several years with left upper quadrant pain following an injury. So many diagnostic procedures had failed to reveal the cause of the pain that he had been generally labeled as a neurotic and malingerer. I was immediately attracted by the patient using the index finger to point to the location of the pain, which was at the outer border of the left upper rectus muscle, and by the marked agony that he appeared to suffer on attempting to rise from the supine position. Because of the extremely sensitive condition of the small area in which he located the pain, it seemed analogous to some other local pains about the head in which excellent results had been obtained by injecting the painful areas with local anesthetic. Immediately after the injection the patient was able to perform any and all movements involving the abdominal muscles without pain. Moreover, the patient reported complete relief for 4 weeks. The pain recurred but was again relieved by injection.

Because of this startling result I have used the injection treatment in many different kinds of pain which seemed to be parietal. In many but not all instances the relief has been equally satisfactory. The following case illustrates the puzzling character of the pain, the ease of diagnosis, and finally the successful treatment.

The important points to learn from this case report are

(1) To suspect parietal pain when the pain is in or near surgical scars;

(2) To suspect parietal pain when contraction of the abdominal muscles is an aggravating factor;

(3) To confirm these impressions by several simple procedures;

(4) To differentiate localized parietal pain from referred, segmental nerve root pain;

(5) That the therapy for the pain is immediately suggested by the diagnostic procedure to be described.

CASE REPORT

A young and healthy appearing girl came to the Clinic on February 25, 1943 complaining of vomiting. She had been in good health until two years previously when she had had an attack of acute appendicitis (proven at operation). Uncomplicated recovery followed appendectomy (short right rectus incision). No drainage was used. However, shortly after discharge from the hospital, she complained of pain and soreness in the lower right quadrant. The pain was greatly aggravated by attempts to rise from the supine position. About 4 months after the onset of the pain the patient began to vomit occasionally when the pain was more severe. The episodes of vomiting increased in frequency, and in the previous 8 months the patient vomited after every meal, about an hour post cibum until recently when it occurred immediately. Most of the food eaten was eructated although the patient did not show the evidence of malnutrition proportional to this history, which aroused the suspicion of functional or neurotic vomiting. The pain in the side was not aggravated by the ingestion of food or bowel function, but the act of vomiting aggravated the pain. No urinary tract symptoms were present.

Physical examination showed a healthy appearing young woman. The only abnormal finding was the extreme pain she appeared to register on the lightest touch to the lower end of the incision. The tenderness was localized to an area the size of a half dollar. Only with the greatest contortions and grimaces of pain could she raise herself straight up from the supine position. Tenderness was extreme when the recti muscles were taut.

The well nourished state and the extreme reaction to pain strongly suggested a functional state, but a thorough study was considered advisable.

A complete gastrointestinal x-ray series was entirely normal. Urograms and plain plates of the kidney area were normal. Stool examination was normal. Basal metabolic rate was minus 3. Eye examination for possible intracranial pressure showed normal fields and fundi.

Laboratory studies showed a normal urine, normal blood count, normal blood sugar, normal blood urea, negative blood Wassermann and Kahn reactions, and two normal examinations of the feces. The examiner finally concluded that, in spite of the negative studies, the patient was not neurotic and referred her to me for a trial injection of the painful area.

It was evident that the pain was parietal and not visceral because it was aggravated rather than relieved when slight pressure was applied with the recti muscles flexed tautly. The skin was extremely hypersensitive (pinching method of testing) over the site of the pain but not over the segmental distribution of the nerve.

Five cc. of 2 per cent procaine solution was injected into the subcutaneous fat and the scar and rectus muscle with one straight plunge of the needle into the center of the

tender area. In one minute the patient experienced complete relief and got up from the examining table without pain.

She was instructed to eat a full meal that evening and the next morning and to report what effect it had on the vomiting. She ate these two meals and also those for two more days without trouble of any kind; then her trouble returned the same as before. Three different times the area was injected with the same results. The local nature of the pain was demonstrated sufficiently for us to advise surgical removal of the scar since the most probably diagnosis was a neuroma in the scar.

On March 21 Dr. F. L. Shively incised the scar completely in the skin and subcutaneous tissue down as far as the muscles. On gross and microscopic examination there was an indurated nodule in the excised specimen the size of a small marble which proved to be an area of fat necrosis, and a small shiny nodule the size of a pea which proved to be a cyst. No evidence of neuroma was found.

The patient's convalescence was uneventful. Today, 10 weeks after operation, the patient is still perfectly well. The explanation of the etiology of such severe pain and reflex vomiting is still a mystery.

An exactly similar case was seen in a young girl with severe pain and vomiting following appendectomy. A diagnosis of a functional state was made by most of the observers who studied the case. Because of the pain in the region of the scar, I favored a diagnosis of adhesions of the omentum or intestines to the parietal peritoneum. After my colleagues had prescribed treatment without success, an exploratory operation was performed at my suggestion, and nothing abnormal was found but the patient never had another pain after the exploratory operation. The complete recovery of the patient remained a mystery to me until the case reported here was solved by the removal of the scar. In this case the incision was at the same site, the scar was dissected out, and unwittingly the patient was cured. This condition occurs frequently and can be easily recognized if suspected. In most cases the symptoms are not so extreme as in the reported case. However, the patients are quite uncomfortable and miserable from the pain especially if their work involves much use of the abdominal muscles.

The most frequent, and the most severe and disabling pains of this character occur in the abdominal muscles or subcutaneous tissues usually along the outer edge of the recti muscles, but other types of parietal pain can also be diagnosed and treated by this method.

The most common sites of pain are (1) the abdominal area in the region of the surgical scar and especially along the outer edge of the recti muscles; (2) the area near the end of the short ribs; (3) the area between and below the scapula; (4) areas in the large low back muscles; and (5) scattered areas too indefinite to classify.

In many cases an injection with a local anesthetic not only gives relief for the few hours of the anesthetic action, but frequently for weeks and

months. The explanation of this phenomenon is not any more clear than the pathology; a doctor with whom I discussed this recently assured me that he was getting similar results with the injection of air.

The etiology of these painful spots would appear to be most logically explained on the basis of trauma. Nearly all cases followed surgery or a fairly definite history of trauma, although at times this may have consisted only of a powerful, sudden contraction of a muscle in the affected area.

Before being aware of the value of injection in these cases, I had 5 cases of disabling pain at the end of the floating ribs under observation at one time Nothing except strapping gave relief, and this was unproductive for any length of time. Such pain is fairly persistent and at times disabling, but one injection at the end of the affected rib frequently gives permanent relief. The same is true of the extremely painful areas occurring about the scapula.

The detection of these spots is best learned by experience, and the rapid injection of novocain has given better relief than the slow infiltration. The use of saline has been suggested but not tried in my experience. The effect of air has been mentioned, which would suggest that the beneficial effect is one of distention rather than of anesthesia.

I am certain that many pains can be diagnosed as being parietal in nature by this method, and if tried early instead of late the procedure will often save more expensive and time-consuming methods. The confirmation of pain in the abdomen as parietal in nature rather than intraabdominal often will save a useless exploratory operation. Furthermore, amazingly quick relief may be appreciated from certain types of pain which never have been relieved by methods previously at my disposal. The relief is often permanent or of sufficient duration for periodic injections to be adequate therapy.

In conclusion, this simple method is presented as a definite aid in the diagnosis and treatment of many discretely localized but indefinite types of pain.

THE MECHANISM OF POSTPUNCTURE HEADACHE

W. JAMES GARDNER, M.D.

Postpuncture headache occurs in perhaps 20 per cent of patients who have had a diagnostic lumbar puncture. It usually begins within 12 hours of the lumbar puncture. The headache is occipital, or occasionally frontal, and appears within a short time after the patient assumes the erect position. Associated symptoms may be nausea or stiffness of the neck. The headache is very distressing and usually incapacitating but is relieved almost immediately by lying down.

The condition is usually ascribed to a loss of cerebrospinal fluid through the needle puncture wound in the dura which removes the fluid cushion supporting the brain, and allows the brain to settle in the cranial cavity causing traction on the nerves, blood vessels, and dura. The headache appears shortly after the patient assumes the erect posture because with this change in position the lumbar fluid pressure is approximately trebled, thus greatly increasing the rate of fluid loss through the puncture wound.

It is a fact that postpuncture headache is accompanied by a decreased volume of cerebrospinal fluid. This can be proved by measuring the quantity of fluid after removing it and replacing it with air as in encephalography. In patients with a postpuncture headache, the spinal pressure is abnormally low, and the volume of cerebrospinal fluid recoverable at encephalography is always greatly reduced. In some cases I have found it to measure as little as 30 cc. as compared with a normal of perhaps 120 cc. This, however, does not prove that the lost cerebrospinal fluid has escaped through the puncture wound in the dura.

To me the puncture wound of the dura does not appear to be the significant factor, but rather the puncture wound of the arachnoid. The following analogy explains the thesis.

The cerebrospinal fluid is contained within the pia-arachnoid membrane which in turn is closely invested by the dura. This system may be compared to an automobile tire with the air representing the cerebrospinal fluid; the inner tube, the pia-arachnoid; and the tire, the dura. The puncture of an automobile tire does not result in any loss of the contained air, but a puncture of the inner tube will permit the air to escape even though the tire itself is intact.

The pia-arachnoid is a closed system like the automobile inner tube. The brain, spinal cord, blood vessels, and nerves are all really outside the

subarachnoid space, being separated from it by the inner layer of the pia-arachnoid. Therefore, there is no break in the pia-arachnoid system where the spinal nerves and blood vessels leave the spinal canal. The dura, on the other hand, like the automobile tire is not a closed system. Although it provides a cuff for the emerging spinal nerves, nevertheless where this cuff ends an opening in the dura allows the exit of the nerves. The dural sac, therefore, although very much heavier than the pia-arachnoid, cannot be considered a water-tight system. By itself, the flimsy arachnoid could no more support the stresses put upon it than could an inner tube support a car without its investing tire. But backed up by the dense inelastic dura the arachnoid is adequate and water-tight.

From the foregoing analogy it is apparent that the cerebrospinal fluid must first escape through the puncture wound in the arachnoid membrane into the subdural space. From here it may pass through the puncture wound in the dura, but probably the greater portion of it is extruded through the intact dura or through the openings in the dura which transmit the spinal nerves. A postpuncture headache can, therefore, persist even after the puncture wound in the dura has closed.

It is very significant that encephalograms performed in patients who have had a recent spinal puncture, especially if they are the victims of a postpuncture headache, may be unsatisfactory for the reason that the injected air is found to be largely in the subdural space rather than in the subarachnoid space and ventricles. This latter finding suggests the mechanism of postpuncture headache as follows:

When a spinal puncture is performed, the needle perforates both the dura and the arachnoid membrane to reach the subarachnoid space. Since the dura is a dense, heavy membrane, the perforation is more apt to close in it than in the arachnoid which consists of a thin, filmy membrane. The opening in the arachnoid membrane permits the subarachnoid fluid to escape into the subdural space with a consequent partial collapse of the arachnoid sac. If this condition exists, that is, if a subdural collection of fluid occurs after spinal puncture, and if an encephalogram is then performed, a free flow of fluid will be obtained as soon as the needle enters the distended subdural space. Because of the free flow of fluid the operator assumes that the needle is in the subarachnoid space and exchanges the fluid for air. The air, however, is injected into the subdural space as the subsequent films will show.

A similar accident may occur with myelography. Hamby[1] has shown that if a lipiodol myelogram is performed following a recent spinal punc-

ture, the myelogram films may be unsatisfactory due to the fact that the lipiodol has been injected into the subdural rather than the subarachnoid space. It is, therefore, a fact that after spinal puncture a quantity of cerebrospinal fluid may pass through the perforation in the arachnoid membrane into the subdural space with a consequent collapse of the arachnoid membrane. Nature did not design the dura to serve the purpose of a water-tight barrier. Therefore, if there is a subdural collection of fluid in the lumbar canal and the patient assumes the erect position, the pressure of the fluid in the subdural space is suddenly tripled or quadrupled. This increased head of pressure causes the fluid to be rapidly extruded, probably in large part along the dural cuff of the spinal nerves. With the extrusion of the fluid the brain is permitted to settle in the cranial cavity with resulting traction on the anchoring blood vessels, nerves, and dura causing headache. When the patient lies down, the brain sag is overcome, and the headache soon disappears.

With the lowering of the spinal fluid pressure which occurs when the supine position is assumed, the subdural fluid is no longer extruded so rapidly, and it once more gradually accumulates.

In the sitting position postpuncture headache will continue as long as there is a subdural accumulation of fluid of any consequence. As soon as the perforation in the arachnoid is closed and the subdural accumulation is extruded from the dural sac, the volume of subarachnoid fluid is restored to normal and the postpuncture headache is relieved.

Postpuncture headache does not occur in every patient following lumbar puncture, because in most individuals a subdural collection of fluid does not take place. Usually, the filmy adhesions between the arachnoid and dura prevent the arachnoid from collapsing so that the subdural space remains as nature intended—a potential space only.

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ADRENAL FAILURE OF PITUITARY ORIGIN

Plasma Protein Studies (Tiselius)

Report of Four Cases

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and WM. F. OWEN, M.D.

In cases of pituitary deficiency in which lack of somatic and skeletal growth is outstanding, it has been customary to speak of pituitary dwarfism or pituitary infantilism despite the obvious coexistence of gonadal deficiency. In the same sense we speak of pituitary myxedema.

By speaking of adrenal failure of pituitary origin we purposely call attention to the fact that many of the serious symptoms of pituitary disease are of adrenal origin and that a great deal can be accomplished by treating the adrenal failure as it is treated in Addison's disease. For some years, we have used adrenal extract in such cases. More recently, the chief therapeutic agents have been desoxycorticosterone acetate the NaCl; adrenal extract, testosterone propionate or methyl testosterone have been added in some cases, and occasionally small doses of thyroid.

The 4 cases reported here are instances of rather severe pituitary failure. We purposely are not calling these cases Simmond's disease because the term suggests the type of acute pituitary damage which was the basis of the condition in Simmond's original cases and emphasizes the feature of emaciation which was not present here. Williams and Wittenberger[1] reported similar cases which they classified as Simmond's disease and treated in much the same way as we have treated ours. Our cases are similar to the type which Albright[2] designated panhypopituitarism, in which he emphasized the pecularities of the glucose and insulin tolerance tests.

The selected cases demonstrate some of the interesting diagnostic features and present methods of treatment. In one case there were peculiar crises characterized by stupor, fever, weakness, vomiting, and hypoglycemia. These episodes were very similar to those present in a case described recently by Dynes,[3] which he believed were the result of hypothalamic pressure. In ours there was little to suggest that hypothalamic pressure existed, and we believe that the attacks were similar to those which occur in the crises of Addison's disease. In the cases presented here studies were made of the protein chemistry which has not previously been described.

CASE REPORTS

Case 1—A 44 year old white clerk complained of an illness which probably began about 5 years ago when he had noticed that he was "below par" generally. He had complained to his physician of frequent colds and weakness and had been given liver injections and iron capsules for "anemia."

During the previous 8 months the patient had experienced increasing weakness and fatigue, both mental and physical. He tended to be excessively sleepy much of the time. During the previous month dizziness had bothered him to the extent that he had found it difficult to walk at times, and 2 weeks before admission he had fainted on the street and had fallen, striking his head and left arm on the pavement. Several times since then he had had to use a support to keep from falling.

His appetite and digestion were moderately good. He was intolerant to cold. The appearance of his skin had not changed. There was no numbness of the extremities, no brittleness of the nails, no falling of hair, nor edema.

Sexual maturity had been incomplete. There had never been any axillary or pubic hair; facial hair was very sparse. Shaving was not necessary more than once or twice a week. Sexual libido and potence had been slight or nil.

Examination showed a rather pale man with a very placid expression with a suggestion of edema (Fig. 1). His height was 65 inches; weight 163 pounds. Temperature and pulse were normal. Blood pressure was 90 systolic and 70 diastolic. He stood with an attitude indicating little energy and showing dorsal kyphosis. The evidence of gonadal failure was obvious. The head hair was profuse; the temporal hairline was not retracted. The supraorbital ridges were small; facies rather immature; the larynx small; and the chest relatively narrow. The genitalia were developed to what might be normal for the age of 16 or 17 years. The testes were small but solid. The prostate gland was about ½ normal size; its borders could scarcely be made out. The hands had a peculiar thickness of the tissues, and the facies suggested the possibility of a previously existing or "fugitive" acromegaly. Neurologic examination showed no evidence of central nervous system disease. The cardiac examination revealed distant heart sounds.

The results of some of the more important laboratory tests and special examinations are indicated in the following table.

TABLE 1

X-ray sella—depression of sellar floor and erosion of posterior clinoids
Visual fields—normal; fundi—normal
Kepler index[4]—12.8 (normal above 25.0)

Glucose tolerance[5]
(mg. glucose per 100 cc. blood)

Hours	F.	½	1	2	3	4
	96	116	99	79	74	74

Insulin tolerance[6]*
(mg. glucose per 100 cc. blood)

Minutes	F.	** 20	30	45	60	90	120	*** 45	60
	76	58	45	40	34	52	56	110	100

* High carbohydrate diet for 3 days preceding test
** 6.8 units insulin intravenously
*** 0.68 cc. adrenalin 1:1000 intramuscularly

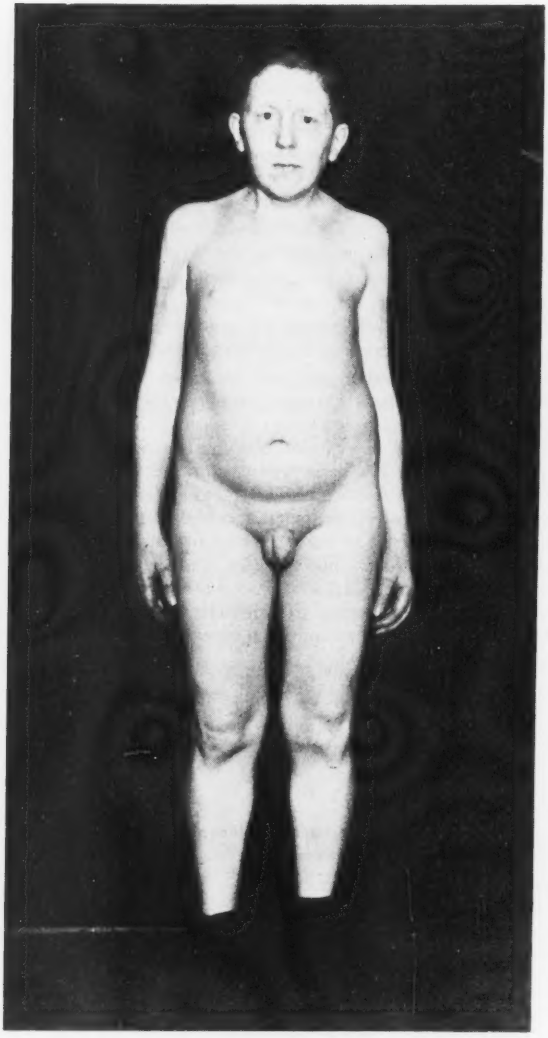


Figure 1. Note immature appearance and genital hypoplasia.

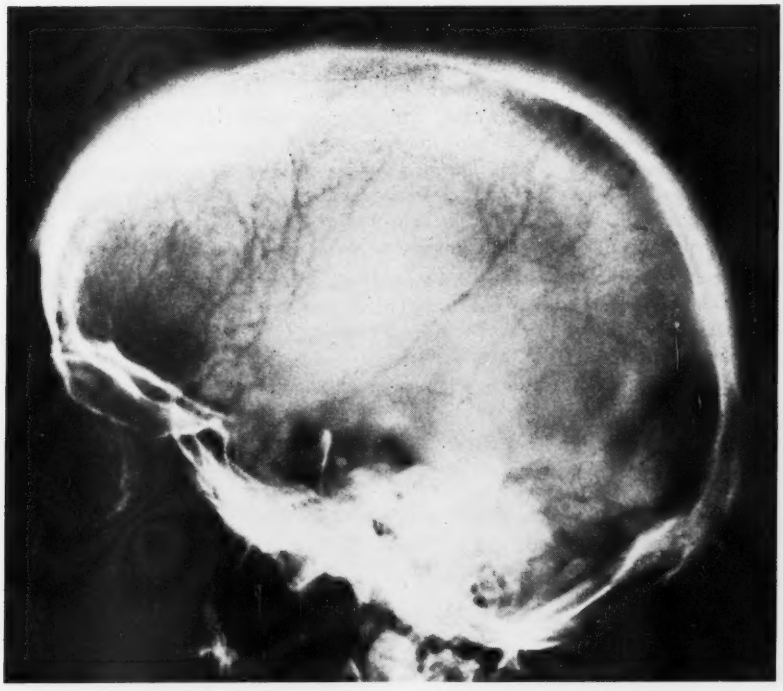


FIGURE 2. Case 1—Depression of sellar floor and erosion of posterior clinoids.

Amino-acid tolerance[7]*

(mg. amino N/100 cc. blood)

Minutes.....	F.	17	23	30	45	60
	6.1	8.8	7.0	6.6	5.8	4.8

* 50 cc. 10 per cent amigen intravenously (Amigen—Mead Johnson & Co.) Amigen is a dried enzymic digest of purified casein and pork pancreas containing amino-acids and polypeptides. The total nitrogen content is 12.0 percent, amino nitrogen 7.4 percent. The above composition is quoted from the manufacturer's claim.

Plasma proteins (Tiselius)[8]

(Gm. per 100 cc. plasma)

Total plasma proteins	Alb.	α Glob.	βGlob.	γ Glob.	Fib.
4-10-43..... 6.85	3.83	0.27	1.34	0.95	0.46

Gonadotropic hormone assays[9] (3)—none measurable

Urinary androgens[10] 2.0 mg./24 hrs. (normal—7.0 to 15.0 mg.)
0.7 mg./24 hrs.

Basal metabolic rate[11]—minus 7 per cent

The serum calcium[12], phosphorus[13], and cholesterol[14]; the red blood cell count and hemoglobin, and urinalysis were within normal limits. The blood Wassermann was negative.

The diagnosis was a calcified tumor within the sella turcica. The pituitary activity was of a very low grade and obviously had been producing very little gonadotrophic hormone since before puberty, causing the prepuberal type of eunuchoidism. There was little evidence of hypothyroidism. The most striking explanation of symptoms lay in the very low blood pressure. Urinary keto-steroids[15] too low to be accounted for by testis failure alone and a positive Kepler test supported the diagnosis of decreased activity of the adrenal cortices. The dramatic response to therapy also favored the diagnosis.

Treatment was begun on April 9, 1943 with 5 mg. injections of desoxycorticosterone acetate* in oil intramuscularly daily. Six Gm. of salt as enteric coated 1 Gm. tablets each day and a relatively high carbohydrate diet with intermediate feedings were also prescribed.

After 3 injections the patient felt very much stronger and had no dizziness. His blood pressure had risen to 126 systolic and 80 diastolic. The dosage of sodium chloride was then increased to 10 Gm. daily. The desoxycorticosterone acetate dose was reduced to 3.5 mg. 3 times weekly by injection. In addition he was given testosterone propionate 25 mg. 3 times weekly to encourage protein retention and muscle development and to promote genital growth and sexual maturity. On May 3 his weight had increased 4 pounds; his blood pressure was 126 systolic and 82 diastolic. Four pellets of 75 mg. each of desoxycorticosterone acetate were implanted subcutaneously. The dose of salt was reduced to 5.0 Gm. daily, and methyl testosterone 30 mg. per day was substituted for the injections of testosterone propionate. The patient was symptom free.

Case 2—A white woman, aged 56, was first seen in July, 1942 with the complaint of severe weakness which confined her to her room and much of the time to her bed. The debility had been troublesome for several years, but more so since an acute illness in May, 1941. That attack, as well as others later, was characterized by fever, stupor, vomiting, weakness, and on several occasions severe hypoglycemia. The fever has always been difficult to explain on a basis of inflammation although a mild upper respiratory tract infection has been thought to be the precipitating factor on two occasions.

The patient was healthy until her marriage at the age of 26. She had 3 pregnancies terminated by therapeutic abortions because of uncontrollable hyperemesis gravidarum. Her fourth pregnancy in 1923, when she was 36 years of age, was allowed to come to term in spite of vomiting throughout the period of gestation. After this last pregnancy she had an acute illness diagnosed influenza, following which she was thought to have developed meningitis. She was stuporous and was said to have been blind for 3 days. The spinal fluid was normal. From an x-ray of the skull a pituitary cyst was diagnosed. Following the spinal puncture her sensorium cleared. After recovery from the acute illness, she did not menstruate again. She lost both axillary and pubic hair which has not returned. Since then she has complained of headaches of an indefinite type; her vision has been less acute than formerly; and she is said by her friends to have been disinterested in any activity which requires physical exertion.

* Cortate—Schering Corp.

In May, 1941 she had an acute illness which was similar to that observed in 1923 and to other attacks since then. For several days she complained of lack of appetite and vague gastrointestinal distress. On May 1 she had an attack of diarrhea. Projectile vomiting developed, and after 4 days of the illness she became very stuporous, her blood pressure was low, and she was extremely weak with a subnormal temperature as low as 95.6 F.

After the second hospital day her temperature rose to 105 F. She was treated with intravenous saline and glucose and blood transfusion. After 2 days the temperature returned to normal. During the acute phase of that illness the white blood count was in the neighborhood of 5000. Albumin was found in the urine on one or two occasions. The agglutination tests for typhoid and paratyphoid were negative. Stool examinations were negative. Spinal fluid was normal. Sedimentation rate was 69 the first hour and 98 the second hour (normal 15 to 20). The blood chloride level was as low as 350 mg. per cent, and the blood sugar was as low as 31 mg. per cent. A few days after the attack her

FIGURE 3. Case 2—Note puffiness of the face, marked freckling of the skin, and hairlessness of the axillae.

basal metabolic rate was minus 36 per cent. Since that time she has taken desiccated thyroid 1 Gm. daily with little relief.

When first seen by one of us (E. P. McC.) in July, 1942 she presented the appearance of a pale, tired-looking woman (Fig. 3). Her skin had a yellowish tint, and her face showed many freckles. Her voice was low. She moved with little energy. Her face had a puffy appearance, decidedly suggestive of myxedema. Her height was 66 inches; her weight 117 pounds; temperature 96.8 F.; pulse 96; blood pressure 115 systolic and 60 diastolic. The thyroid gland was not palpable. The breasts were flat and atrophic with very little palpable breast tissue. The nipples and areolae appeared completely without pigment. There was virtually no axillary nor pubic hair. The skin of the body was slightly dry, fine in texture, and was not so thick as is usually seen in myxedema. The heart sounds were rather distant. The external genitalia were atrophic; the vagina small; the vaginal mucous membranes smooth and atrophied. The uterus and cervix were very small, and the vaginal smears were typical of a castrate type. The muscles generally lacked tone. No abnormalities were found on neurologic examination.

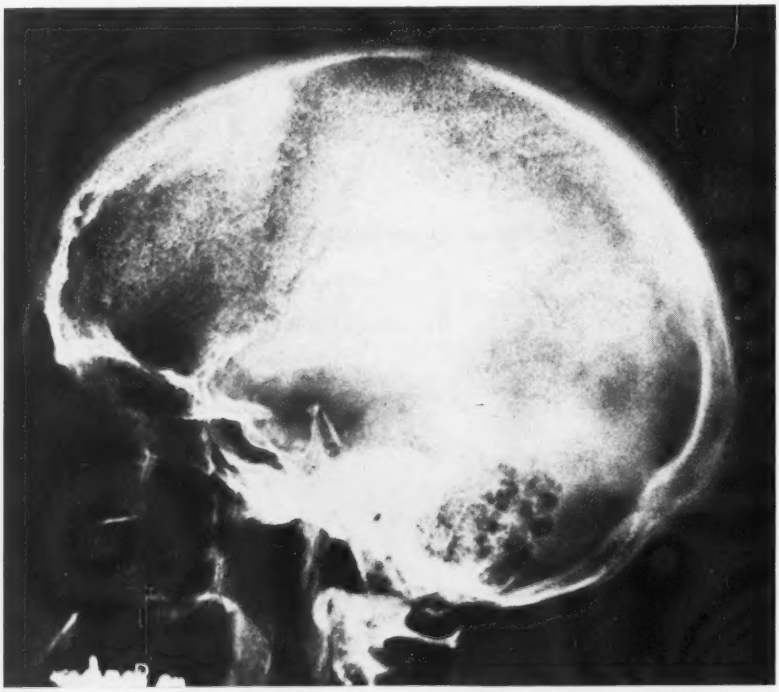


Figure 4. Case 2—Intrasellar calcification.

The results of the more pertinent special examinations were as follows:

TABLE 2

X-ray sella—rather marked intrasellar calcification (Fig. 4)
Visual fields—normal; fundi—normal
Kepler index—11.4 to 6.9 (normal above 25)

Glucose tolerance
(mg. glucose per 100 cc. blood)

Hours.....	F.	1	2	3
	60	147	124	78

Insulin tolerance*
(mg. glucose per 100 cc. blood)

Minutes.....	F.**	20	30	60	120***	45	60
	84	40	37	37	39	64	64

* High carbohydrate diet for 3 days preceding test
** 6.8 units insulin intravenously
*** 0.68 cc. adrenalin 1:1000 intramuscularly

Plasma protein (Tiselius)
(Gm. per 100 cc. plasma)

Total plasma proteins	Alb.	α Glob.	β Glob.	γ Glob.	Fib.
5-28-43..... 5.97	3.12	0.36	1.04	1.12	0.33

Urinary androgens—none measurable
Basal metabolic rate—minus 36 per cent
Serum cholesterol—145 mg. per cent
Red blood count—3,700,000 per cu. mm.
Hemoglobin—9 Gm. per 100 cc.
The serum calcium and phosphorus were within normal limits; urinalysis was also normal. The blood Wassermann was negative.

The diagnosis was intrasellar lesion producing rather severe pituitary gland failure. Myxedema of the pituitary type was suspected, although her lack of improvement on thyroid mediciation made it very doubtful. However, she obviously had a very severe ovarian deficiency and a relatively severe adrenocortical hypofunction. Adrenal cortical deficiency was indicated by the low Kepler index, abnormal insulin tolerance, and the absence of urinary androgens. There was also a rather marked hypochromic anemia. Her improvement and progress have been excellent on the treatment outlined until recently when she experienced another acute episode or crisis similar to those which she had in 1923, May, 1941 and in November, 1942. This recent attack was as follows:

She had increasing stupor for 3 days, complained of mild headache, and vomited repeatedly. It was thought at first that she had a very slight cold, but none could be demonstrated on hospital admission. Her temperature was 103.1 F.; pulse 110; blood pressure 110 systolic and 40 diastolic; respirations were normal. Her white blood count was 6250 per cu. mm.; red count 4,300,000; and hemoglobin 71 per cent, or 11 Gm. per 100 cc. Her blood urea was 39 mg. per cent; the chlorides were somewhat below normal, being 490 mg. per cent; blood sodium was consistent with that found in Addison's disease, being 308 mg. per cent. The blood potassium was within normal limits at 17.7 mg. per cent. Urinalysis was normal. There was no evidence of an inflammatory lesion

sufficient to cause this reaction. She was treated with adrenal extract* in doses of 10 to 20 cc. per day.

Intravenous glucose in saline was given, and she was fed with an intranasal tube supplying approximately 2100 calories per day. The 53 Gm. protein which was given daily by this method was supplemented with amino-acids by mouth in the amount of about 30 Gm. daily. The temperature steadily decreased for 3 days and on the fourth day was as low as 95.6 F. It was subnormal most of the time during the next 2 weeks.

Treatment was started in August, 1942. A diet was prescribed which contained 300 Gm. of carbohydrate per day. Extra feedings were given between meals and at bed time. Sodium chloride was given in enteric coated tablets 4 Gm. daily, and desoxycorticosterone acetate in injections of 2 mg. per day. In addition she continued with the use of desiccated thyroid 1 gr. per day and ferrous sulfate. In September, 1942 her blood pressure had risen to 130 systolic and 88 diastolic; her weight had increased about 6 pounds. The puffiness of the face suggesting myxedema did not disappear with the use of thyroid. In September, 1942 four 75 mg. desoxycorticosterone pellets, the shape of cylinders, were implanted subcutaneously. Her improvement was striking. From October to December, 1942 extra adrenal extract† was administered by mouth, one tablet 3 times daily, but produced no noticeable clinical change.

Her weight increased to 123 pounds, and the blood pressure rose to 140 systolic and 100 diastolic when the extra sodium chloride was discontinued. Her weight and blood pressure were maintained at normal. Her blood count rose to 4,620,000 red cells per cu. mm. and 11 Gm. per 100 cc. (71 per cent) of hemoglobin. Her strength was good, and she was free of symptoms and able and anxious to undertake more activity than she had for years, until her progress was interrupted by the recent crisis which has been described. Because of the extremely low assay for androgens, she was given methyl testosterone 10 mg. per day orally for several weeks, but this made little if any change in her symptoms and was discontinued. Her present treatment includes desoxycorticosterone pellet implants, thyroid and extra sodium chloride daily as before, and 4 cc. of adrenal extract†† per day.

Case 3—A 39 year old steam engineer claimed good health until one month before admission, when he noted weakness and anorexia. His own physician had diagnosed streptococcus throat infection, but no cultures had been taken. His symptoms had been characterized by slight fever and sore throat for one week. Weakness, marked fatigue, anorexia together with mild abdominal distress persisted. He had lost 11 pounds in weight during the month previous to admission and was unable to work.

The past history and systemic review revealed that puberty had been somewhat later than average; libido and potence were minimal but unchanged recently.

Examination showed a pale, slightly obese, rather stooped man who showed little evidence of normal energy. His height was 65.5 inches, weight 179 pounds. His span was 69 inches. He was somewhat bald, had very little chest and axillary hair, and the pubic hair was in feminine distribution (Fig. 5). The penis was less than average size, and the testes were small but perhaps within the range of normal. The prostate was less than average in size. The important special examinations and laboratory tests are summarized in Table 3.

* Eschatin (50 d.u./cc)—Parke Davis & Co.

† Cortalex—Upjohn Co.

†† Adrenal extract(50 d.u./cc)—Upjohn.

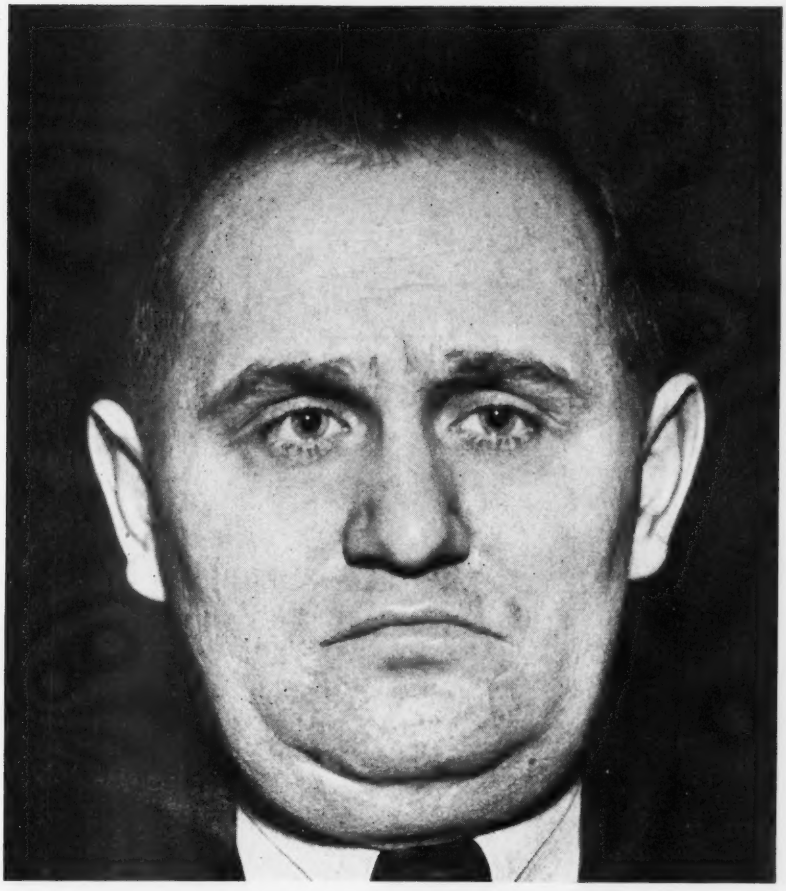


FIGURE 5. Case 3—The appearance is placid, the color sallow, and the eyes show slight evidence of residual ocular muscle weakness.

TABLE 3

X-ray sella—enlargement with elevation and erosion of posterior clinoids (Fig. 6)
Visual fields—bitemporal hemianopsia for form and color; fundi—temporal pallor of discs
Kepler index—1.4 (normal above 25.0)

Glucose tolerance
(mg. glucose per 100 cc. blood)

Hours	F.	½	1	2	3	4
	113	193	176	150	133	85

Plasma protein (Tiselius)
(Gm. per 100 cc. plasma)

Total plasma proteins	Alb.	α Glob.	β Glob.	γ Glob.	Fib.
3–18–43..... 6.57	3.02	0.39	1.58	0.99	0.59

Gonadotrophic assay—none measurable
Urinary androgens—2.6 mg./24 hrs. Dec. 1940 (normal 7 to 15)
12 international units (capon test) (normal 18 to 80)
6.0 mg./24 hrs. April, 1943
1.5 mg. (Ketonic fraction)

Basal metabolic rate—minus 15 per cent
Red blood count—4,200,000 per cu. mm.
Hemoglobin—12.5 Gm. per 100 cc.
Serum calcium and urinalysis were normal.

Clinically, this patient was suspected of having a pituitary tumor. This was corroborated by x-ray and perimetric examinations. Complete absence of measurable gonadotropic hormone by the rat test is unusual in men. This plus the clinical evidence of

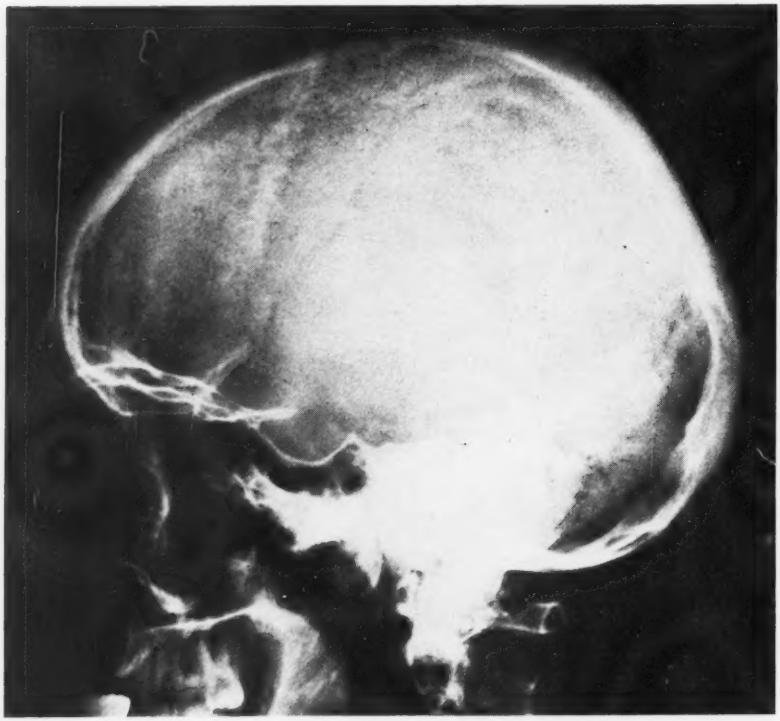


Figure 6. Case 3—Enlargement of the sella turcica with elevation and erosion of posterior clinoids.

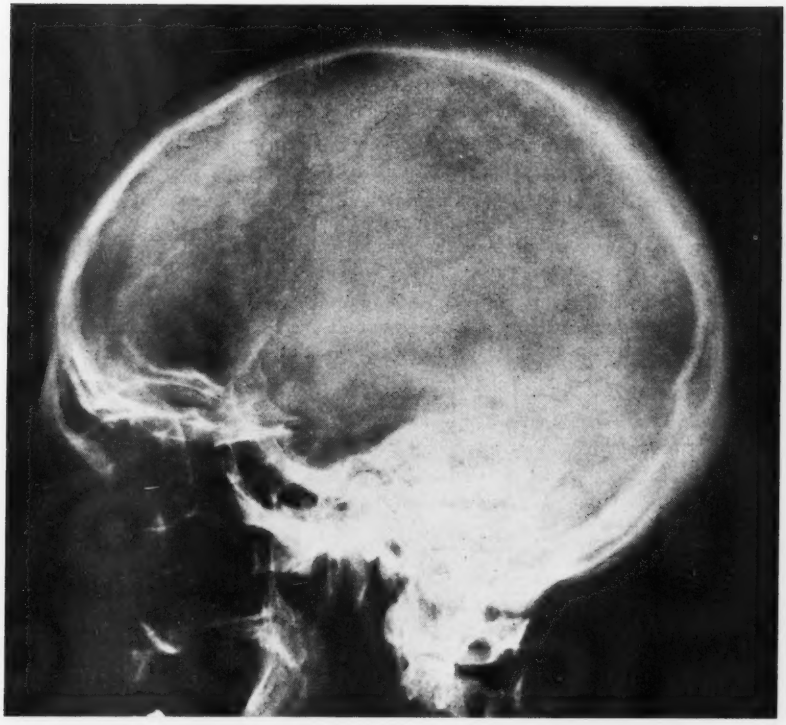


FIGURE 7. Case 4—Erosion of the sellar floor and posterior clinoids.

hypogonadism and very low assays for androgens both by bio-assay and by colorimetric test indicated testicular failure of pituitary origin. The androgen levels were lower here than are seen in gonadal failure alone and indicated the second source of androgens, namely the adrenals, were also deficient. The presence of adrenal deficiency was corroborated by the positive Kepler test. The abnormal plasma proteins simulated those seen in Addison's disease and appeared consistent with this view.

Treatment. X-ray therapy to the pituitary gland was administered daily for 2 weeks. Each treatment consisted of 200 r to three portals. In addition, he received thyroid gr. 1 daily, testosterone propionate 25 mg. 3 times weekly by injection, and 6 to 9 Gm. enteric coated salt tablets daily. He improved moderately on the above treatment. Libido increased, and strength was somewhat better. Desoxycorticosterone acetate in 5 mg. doses 3 times weekly was added, and his general vigor and strength were much improved. Later, a second course of x-ray therapy was given. The visual fields became normal. Testosterone propionate was changed to methyl testosterone 30 mg. daily by mouth. Improvement continued, and when last seen in April, 1943 he was able to carry on his regular occupation and was feeling better than he had in years.

Case 4—A 45 year old man complained of "weakness and anemia." The present illness began 9 years before admission at which time he complained of loss of energy and endurance. For 5 months preceding admission the weakness and exhaustion were extreme. He found himself exhausted after walking 6 city blocks. The referring physician diagnosed anemia and questioned the possibility of Addison's disease.

The past history and systemic review were noncontributory.

Physical examination disclosed a well developed and well nourished, but extremely pale, individual. Height was 69 inches and weight 151 pounds. Temperature was 98.2 F.; pulse 72; and blood pressure 120 systolic and 85 diastolic. Aside from the marked pallor of the skin and mucous membranes, the physical examination was within normal limits. There were no significant pigmentary changes of the skin. The genitalia appeared normal.

The diagnosis of cryptic anemia, possibly resulting from carcinoma of the gastrointestinal tract, kidney, or from multiple myeloma was seriously considered. The pertinent laboratory studies are indicated in the following table.

TABLE 4

X-ray sella—marked erosion of floor and posterior clinoids (Fig. 7)
Visual field—left superior quadrant defect, discs hazy

Glucose tolerance
(mg. glucose per 100 cc. blood)

Hours.....	F.	½	1	2	3	4
	94	124	101	89	86	65

Insulin tolerance
(mg. glucose per 100 cc. blood)

Minutes.....	F.*	20	30	40	60	120	**	45	50
	83	48	37	37	42	61		125	125

*6.8 units insulin intravenously
**0.68 cc. adrenalin 1:1000 intramuscularly

Amino-acid tolerance*
(mg. amino N/100 cc. blood)

Minutes.....	F.	15	20	30	45	60
	6.1	9.6	8.5	6.0	5.2	5.2

* 50 cc. 10 per cent amigen intravenously

Plasma Protein (Tiselius)
(Gm. per 100 cc. plasma)

Total plasma proteins	Alb.	α Glob.	β Glob.	γ Glob.	Fib.
3–5–43..... 6.49	3.88	0.36	1.25	0.56	0.45
4–6–43..... 6.64	3.67	0.46	0.98	1.04	0.49
5–26–43..... 6.35	3.72	0.49	0.95	0.82	0.36

Urinary androgens—3 mg./24 hrs.
1.9 mg. 24 hrs. (Ketonic fraction)
Basal metabolic rate—minus 20 per cent
Red blood count 4,330,000 per cu. mm.
Hemoglobin—11.5 Gm. per 100 cc.
Serum calcium, x-ray of chest and gastrointestinal tract, and urinalysis were normal.

The final diagnosis was pituitary neoplasm with anterior lobe failure and adrenal and gonadal deficiency. In spite of lack of clinical evidence to support the diagnosis of adrenal cortical failure, the positive Kepler test and response to treatment left little doubt that this was present. The urinary androgen was so low as to indicate both adrenal and testis failure, although this was not clinically evident.

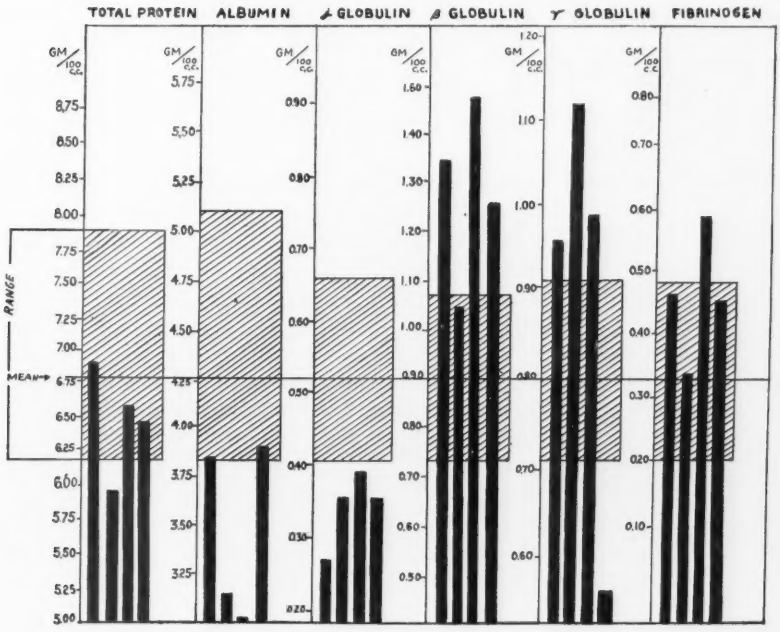
Treatment consisted of a 3 weeks' course of deep x-ray therapy to the pituitary gland, ferrous sulfate gr. 15 daily, 6 to 9 Gm. enteric coated NaCl tablets daily, desoxycorticosterone acetate 1 mg. daily, and testosterone propionate 25 mg. 3 times weekly. On April 7, 1943 300 mg. of desoxycorticosterone acetate was implanted as 75 mg. pellets. At this time the blood pressure went as high as 150 systolic and 90 diastolic, and he experienced episodes of hypoglycemia. Since then he has used only enteric coated salt tablets, ferrous sulfate, and methyl testosterone 30 mg. daily. Under this treatment improvement has been gradual, definite, and progressive. He is able to carry on his regular employment but has less than normal energy and endurance, due chiefly we believe to recurrent hypoglycemia.

COMMENT

All 4 cases had evidence of an organic pituitary lesion. In addition the outstanding symptom in each case was weakness, and in case 1

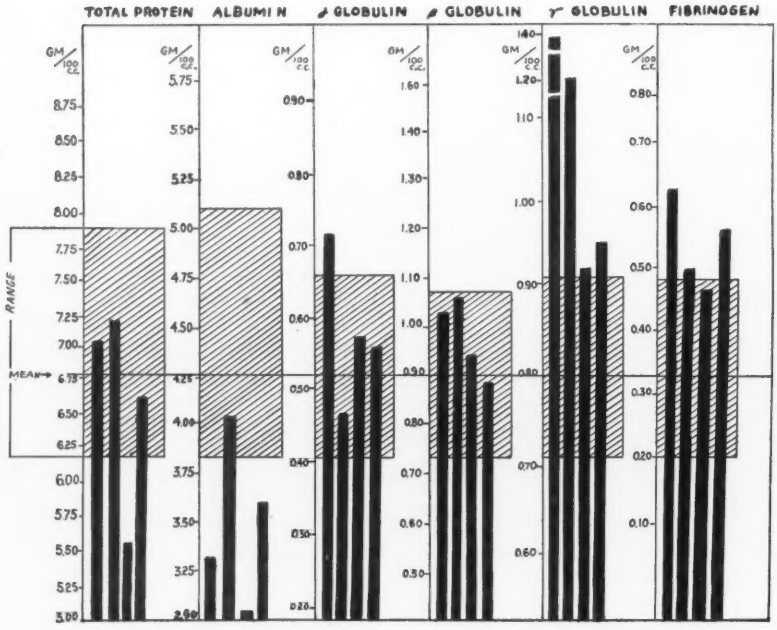
PLASMA PROTEIN FRACTIONS

Adrenal Failure Secondary to Hypopituitarism



PLASMA PROTEIN FRACTIONS

Addison's Disease



weakness and faintness. In case 2 crises occurred which simulated those sometimes seen in Addison's disease.

The evidence of adrenal failure included the very low urinary androgens and the positive water excretion test in all 4 cases. The Kepler test yielded figures of 1.4 to 12.8, while the normal is 25 or over. This result was produced because of the marked delay in water excretion, no striking abnormality being shown in blood or urinary urea or chlorides in any of the cases. Serum sodium and potassium levels were normal on repeated occasions in cases 1 and 4. In case 2 the blood sodium level was 308 mg. per cent on one occasion during a crisis. Hematocrit levels were not remarkable in any of the cases.

The glucose tolerance was not abnormal in any case. In such cases at times an abnormality in this phase of metabolism can be best demonstrated by the intravenous tolerance test and by carrying the test on for a 3 or 4 hour period which may indicate any lack of gluconeogenesis. Insulin tolerance was estimated in 3 cases, and in all the blood sugar

level failed to rise to normal fasting levels in 2 hours. In cases 1 and 2 the test was preceded, as it should be, by a high carbohydrate diet for 3 days. In case 4 this was not possible.

Response to therapy in each case supported the contention that adrenal failure did exist. In case 1 it was dramatic. In case 2 it was excellent but was not capable of preventing the recurrence of crises. In cases 3 and 4 the results were very good and controlled the symptoms well enough so that the patient could work regularly.

Plasma protein studies were made in these 4 cases using the Tiselius electorphoretic technic as modified by Longworth[16]. In 3 of the 4 cases the total protein was in the lower limits of the normal range, in case 2 it was abnormally low. The albumin and α globulin were decreased while the other globulin fractions β and γ and fibrinogen were within normal limits or increased. These results are in contrast with those obtained in Addison's disease showing adrenal insufficiency. In the latter the albumin is decreased, but the α globulin is within normal limits or slightly increased. The normal plasma protein values obtained in this laboratory are in close agreement with those reported by Longsworth[16] et al and Swensson.[17] These results will be published in detail later.

In all normals the amino N level had fallen to the fasting level, or below, 30 minutes after the beginning of the injection. In the 2 patients

Normal Amino-acid Tolerance
(mg. amino N/100 cc. blood)

Minutes.....	F.	15	20	30	45	60
	5.6	8.8	6.8	5.4	5.4	5.6

in this series in whom amino-acid tolerance tests were done, there was no significant deviation from the normal.

SUMMARY

Four cases are presented showing evidence of organic pituitary lesions. In each there are symptoms and laboratory evidence to indicate the presence of adrenal cortical deficiency.

Amino-acid tolerance and plasma protein levels (Tiselius) are similar to those observed in cases of Addison's disease, but differ somewhat in the height of the α globulin fraction.

Response to treatment with desoxycorticosterone was good in each case. Adrenal extract, testis hormone, and thyroid were used as adjuncts to therapy. The results of treatment were better than we have been able to secure with other forms of therapy in similar cases.

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